

THIONE DERIVATIVES, PROCESSES FOR THE PREPARATION  
THEREOF, AND PHARMACEUTICAL COMPOSITIONS CONTAINING  
THE SAME

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5 Technical Field

The present invention relates to a thione derivative or a non-toxic salt thereof which is effective in reduce inflammation, pain, or fever, a method for preparing the same, and a pharmaceutical composition containing the same as an active ingredient.

10

Background Art

15

Most nonsteroidal antiinflammatory agents are responsible for blocking enzyme, cyclooxygenase (COX) or prostaglandin G/H synthase, to reduce inflammation, pain, or fever. In addition, they inhibit uterus contraction caused by hormones and also inhibit growth of several cancers. Cyclooxygenase-1 (COX-1) was first discovered in bovine. The COX-1 is constitutively expressed in a variety of cell types. Unlike the COX-1, cyclooxygenase-2 (COX-2) is a recently discovered isoform of cyclooxygenase that can be easily induced by mitogen, endotoxin, 20 hormone, growth factor, or cytokine.

25

Prostaglandin is a potent mediator for various pathological and physiological processes. The COX-1 plays important physiological roles such as in the release of endogenous prostaglandin, the maintenance of the shape and the function of stomach, and the blood circulation in the kidney. On the other hand, the COX-2 is induced by an inflammatory factor, hormone, a growth factor, or cytokine. Therefore, the COX-2 is involved in pathological processes of prostaglandin, unlike the constitutive COX-1. In this regard, selective inhibitors of the COX-2 produce fewer and less side effects in terms of action mechanism in comparison with conventional nonsteroidal antiinflammatory agents. In addition, they reduce inflammation, pain, and fever and inhibit uterus contraction caused by hormones and growth of several cancers. In particular, they are effective in decreasing side effects such as stomach toxicity and kidney toxicity. Still furthermore, they inhibit the synthesis of 30 contractile prostanoid, thereby leading to suppression of the contraction 35

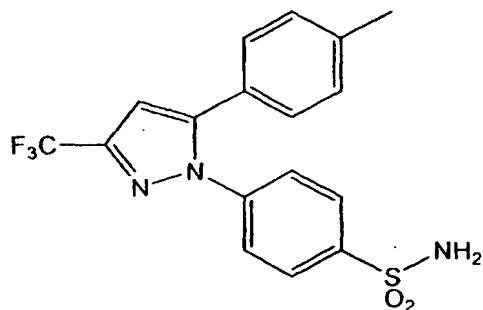
In addition, it is anticipated that selective inhibitors of the COX-2 would be effective in treating osteoporosis and glaucoma. Utility of selective inhibitors of the COX-2 is well described in publications [John Vane, "Towards a Better Aspirin" in *Nature*, Vol.367, pp215-216, 1994; 5 Bruno Battistini, Regina Botting and Y.S. Bakhle, "COX-1 and COX-2: Toward the Development of More Selective NSAIDs" in *Drug News and Perspectives*, Vol.7, pp501-512, 1994; *Urology*, Vol.58, pp127, 2001; David B. Reitz and Karen Seibert, "Selective Cyclooxygenase Inhibitors" in *Annual Reports in Medicinal Chemistry*, James A. Bristol, Editor, Vol. 10 30, pp179-188, 1995].

Various selective COX-2 inhibitors having different structures are known. Among them, a selective COX-2 inhibitor having a diaryl heterocyclic structure, i.e. a tricyclic structure has been widely studied as a potent candidate. The diaryl heterocyclic structure has a central ring and a sulfonamide or methylsulfone group attached to one of the aryl rings. 15

One selective COX-2 inhibitor, Celecoxib of formula 87 is disclosed in U.S. Patent No. 5,466,823. The Celecoxib is a substituted pyrazolyl benzenesulfonamide derivative.

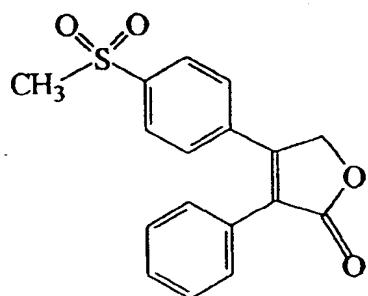
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Formula 87



Another selective COX-2 inhibitor, Rofecoxib of formula 88 is 25 disclosed in WO 95/00501. The Rofecoxib has a diaryl heterocyclic structure with a central furanone ring.

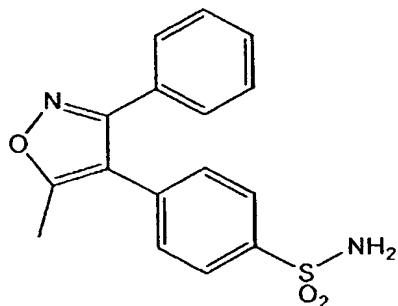
Formula 88



Valdecoxib of formula 89 as another selective COX-2 inhibitor is disclosed in U.S. Patent No. 5,633,272. The Valdecoxib has a phenylsulfonamide moiety with a central isoxazole ring.

5

Formula 89



10 The selective COX-2 inhibitors of formulas 87 to 89 are effective inflammatory therapeutic agents with fewer and less side effects in comparison with conventional nonsteroidal antiinflammatory agents.

#### Disclosure of the Invention

15 An aspect of the present invention provides a thione derivative of formula 1 or a non-toxic salt thereof.

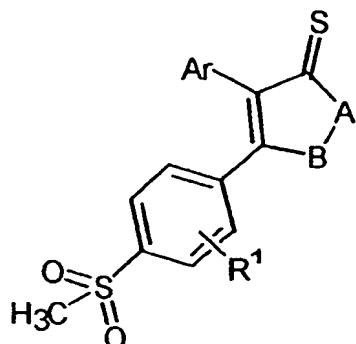
Another aspect of the present invention provides a method for preparing a thione derivative or a non-toxic salt thereof.

20 Another aspect of the present invention provides a pharmaceutical composition comprising a thione derivative or a non-toxic salt thereof as an active ingredient for the treatment of fever, pain, and inflammation.

Best mode for carrying out the Invention

According to an aspect of the present invention, there is provided a thione derivative represented by formula 1:

Formula 1



5

wherein:

A and B each independently represent O, S, NR<sup>2</sup>; wherein R<sup>2</sup> represents hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkenyl, or aryl;

Ar represents aryl; heteroaryl; aryl or heteroaryl substituted with one to five radicals independently selected from the group consisting of C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, trifluoromethyl, nitro, acetoxy, amino, C<sub>1</sub>-C<sub>3</sub> alkylamino, C<sub>1</sub>-C<sub>3</sub> dialkylamino, hydroxy, C<sub>1</sub>-C<sub>3</sub> hydroxyalkyl, and thioxy; and

R<sup>1</sup> represents hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, cyano, nitro, hydroxy, amino, C<sub>1</sub>-C<sub>4</sub> alkylamino, or C<sub>1</sub>-C<sub>4</sub> dialkylamino; or a non-toxic salt thereof.

Preferably, A and B each independently represent S or NH;

Ar represents phenyl; phenyl substituted with one to five radicals independently selected from the group consisting of C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, trifluoromethyl, acetoxy, and nitro; pyridyl; or naphthyl; and

R<sup>1</sup> represents hydrogen or halogen.

The thione derivative of formula 1 may be present in a form of a non-toxic salt. The term, "non-toxic salt" as used herein refers to a pharmaceutically acceptable, toxin-free salt, including an organic salt and an inorganic salt.

The thione derivative of formula 1 may be present in a form of an organic acid salt or an inorganic acid salt.

Examples of the organic acid salt or the inorganic acid salt of the thione derivative of formula 1 include, but are not limited to, a salt of acetic acid, adipic acid, aspartic acid, 1,5-naphthalene disulfonic acid, benzene sulfonic acid, benzoic acid, camphor sulfonic acid, citric acid, 5 1,2-ethane disulfonic acid, ethane sulfonic acid, ethylenediaminetetraacetic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, hydroiodic acid, hydrobromic acid, hydrochloric acid, icethionic acid, lactic acid, maleic acid, malic acid, madelic acid, methane sulfonic acid, mucinic acid, 10 2-naphthalenedisulfonic acid, nitric acid, oxalic acid, pentothenic acid, phosphoric acid, pivalric acid, propionic acid, salicylic acid, stearic acid, succinic acid, sulfuric acid, tartaric acid, p-toluene sulfonic acid, undecanoic acid, and 10-undecenoic acid. Preferably, a salt of succinic acid, hydrobromic acid, hydrochloric acid, maleic acid, methanesulfonic acid, phosphoric acid, sulfuric acid, or tartaric acid is used.

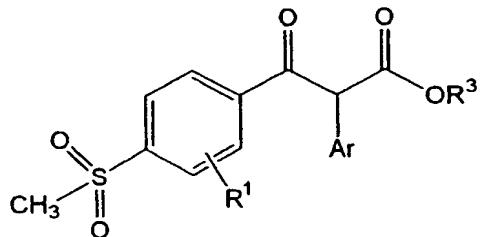
The thione derivative of the present invention preferably includes:  
4-(4-ethoxyphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;  
4-(4-bromophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thio  
ne;  
4-(4-methanesulfonylphenyl)-4-toryl-[1,2]dithiol-3-thione;  
20 5-(4-methanesulfonylphenyl)-4-phenyl-[1,2]dithiol-3-thione;  
5-(4-methanesulfonylphenyl)-4-methoxyphenyl-[1,2]dithiol-3-thion  
e;  
25 5-(4-methanesulfonylphenyl)-4-(2-trifluoromethylphenyl)-[1,2]dithio  
l-3-thione;  
4-(4-chlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thion  
e;  
30 4-(3,4-dichlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-t  
hione;  
5-(4-methanesulfonylphenyl)-4-pyridine-4-yl-[1,2]dithiol-3-thione;  
5-(4-methanesulfonylphenyl)-4-pyridine-3-yl-[1,2]dithiol-3-thione;  
35 5-(4-methanesulfonylphenyl)-4-pyridine-2-yl-[1,2]dithiol-3-thione;  
4-(4-fluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thion  
e;  
4-(2,5-dimethoxyphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-  
3-thione;

4-(3,5-dimethylphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;  
5-  
5-(4-methanesulfonylphenyl)-4-(3-methoxyphenyl)-[1,2]dithiol-3-thione;  
5  
5-(4-methanesulfonylphenyl)-4-(2-nitrophenyl)-[1,2]dithiol-3-thione;  
;  
5-(4-methanesulfonylphenyl)-4-(3-trifluoromethylphenyl)-[1,2]dithiol-3-thione;  
5-  
5-(4-methanesulfonylphenyl)-4-o-toryl-[1,2]dithiol-3-thione;  
10  
4-(2-chlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;  
e;  
4-(2,4-dichlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;  
15  
4-(2-chloro-4-fluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;  
4-(3,4-dimethoxyphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;  
3  
4-(2-bromophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;  
20  
4-(2-fluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;  
4-(2,4-difluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;  
25  
4-(3,4-difluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;  
5-(4-methanesulfonylphenyl)-4-naphthalene-2-yl-[1,2]dithiol-3-thione;  
5-  
5-(4-methanesulfonylphenyl)-4-pentafluorophenyl-[1,2]dithiol-3-thione;  
30  
4-(4-isopropoxylphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;  
5-(4-methanesulfonylphenyl)-4-(4-propoxyphenyl)-[1,2]dithiol-3-thione;  
35  
acetic acid 4-[5-(4-methanesulfonylphenyl)-3-thioxo-3H-[1,2]dithiol-4-yl]phenyl ester;  
5-(2-chloro-4-methanesulfonylphenyl)-4-(4-ethoxyphenyl)-[1,2]dithiol-3-thione;

5-(2-chloro-4-methanesulfonylphenyl)-4-p-toryl-[1,2]dithiol-3-thione  
e;  
4-(4-bromophenyl)-5-(2-chloro-4-methanesulfonylphenyl)-[1,2]dithi  
ol-3-thione;  
5 5-(2-chloro-4-methanesulfonylphenyl)-4-(4-methoxyphenyl)-[1,2]di  
thiol-3-thione:  
5-(3-fluoro-4-methanesulfonylphenyl)-4-p-toryl-[1,2]dithiol-3-thione  
;  
5-(3-fluoro-4-methanesulfonylphenyl)-4-(4-methoxyphenyl)-[1,2]dit  
10 hiol-3-thione;  
acetic acid 4-[5-(3-fluoro-4-methanesulfonylphenyl)-3-thioxo-3H-  
[1,2]dithiol-4-yl]-phenyl ester;  
5-(4-methanesulfonylphenyl)-4-p-toryl-1,2-dihdropyrazole-3-thion  
e;  
15 4-(3,4-dichlorophenyl)-5-(4-methanesulfonylphenyl)-1,2-dihdropyr  
azole-3-thione; and  
4-(4-chlorophenyl)-5-(4-methanesulfonylphenyl)-1,2-dihdropyraz  
ole-3-thione.

According to another aspect of the present invention, there is  
20 provided a propionic acid derivative as an intermediate for the synthesis  
of the thione derivative of formula 1, as represented by formula 2:

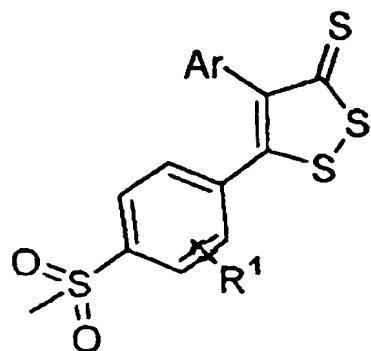
Formula 2



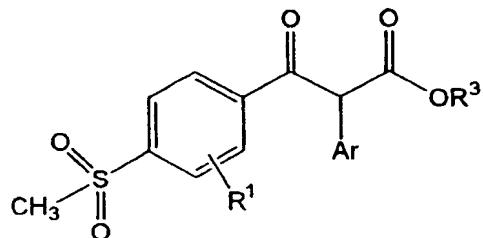
wherein, R<sup>1</sup> and Ar are as defined in formula 1 and R<sup>3</sup> represents  
25 C<sub>1</sub>-C<sub>4</sub> alkyl.

According to another aspect of the present invention, there is  
provided A method for preparing a thione derivative of formula 1a or a  
non-toxic salt thereof, comprising reacting a propionic acid derivative of  
formula 2 with phosphorus pentasulfide, Lawesson's Reagent,  
30 beta-oxothioctic acid, or potassium beta-oxothioctate:

### Formula 1a



### Formula 2



R<sup>1</sup> and Ar are as defined in claim 1;

$R^3$  represents  $C_1$ - $C_3$  alkyl.

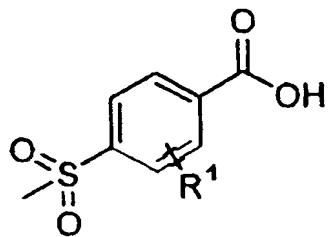
Among phosphorus pentasulfide, Lawesson's Reagent, beta-oxothioxic acid, or potassium beta-oxothiocate, which is used to introduce thione structure, phosphorus pentasulfide is most preferred.

The said reaction is commonly carried out in an unreactive organic solvent, which includes but is not limited to benzene, toluene, and xylene. Among them, toluene is most preferred.

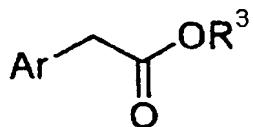
The said reactions may be completed by heating the solvent to its boiling point. For example, when toluene is used as a solvent, the reaction may be completed by heating toluene to the boiling point and refluxing it.

The above propionic acid derivative of formula 2 may be prepared by reacting a methanesulfonylbenzoic acid derivative of formula 3 with a 20 aryl acetate derivative of formula 4 in the presence of a base;

Formula 3



Formula 4



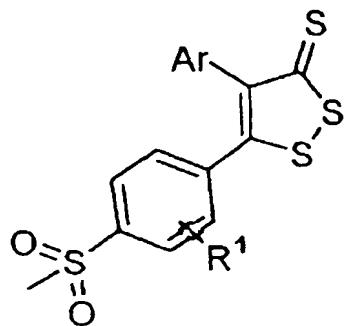
5       wherein, R<sup>1</sup> and Ar are as defined in formula 1 and R<sup>3</sup> represents C<sub>1</sub>-C<sub>4</sub> alkyl.

The said base includes, but is not limited to sodium hydride, potassium carbonate, or potassium hydroxide. Preferably, sodium hydride is used.

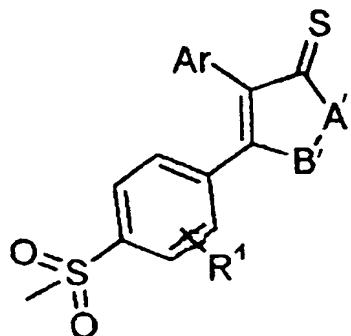
10      According to another aspect of the present invention, there is provided a method for preparing a thione derivative of formula 1b or a non-toxic salt thereof, comprising reacting a thione derivative of formula 1a with NHR<sup>2</sup>NHR<sup>2</sup> or NHR<sup>2</sup>OH in the presence of a base:

15

Formula 1a



## Formula 1b



wherein, A' and B' each independently represent S or NR<sup>2</sup>, provided that A' and B' are not simultaneously S; and Ar and R<sup>2</sup> are as defined in formula 1.

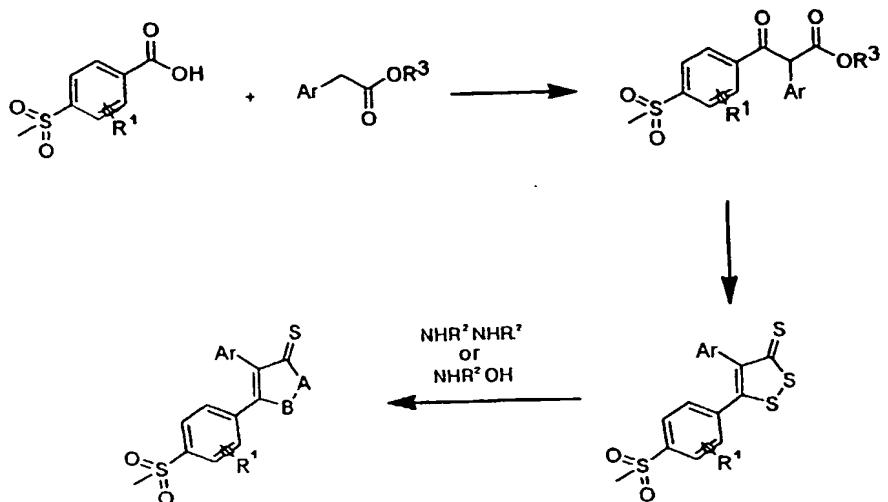
The said base includes, but is not limited to calcium carbonate, potassium hydroxide, or sodium hydroxide. Preferably, potassium hydroxide is used.

The separation and purification of the reaction products can be performed by concentration, extraction, or other processes, which is conventionally used in organic synthesis process, and optionally by a silica gel column chromatography.

A preferred embodiment of the method for preparing a compound of formula 1a and formula 1b is expressed by the following scheme 1:

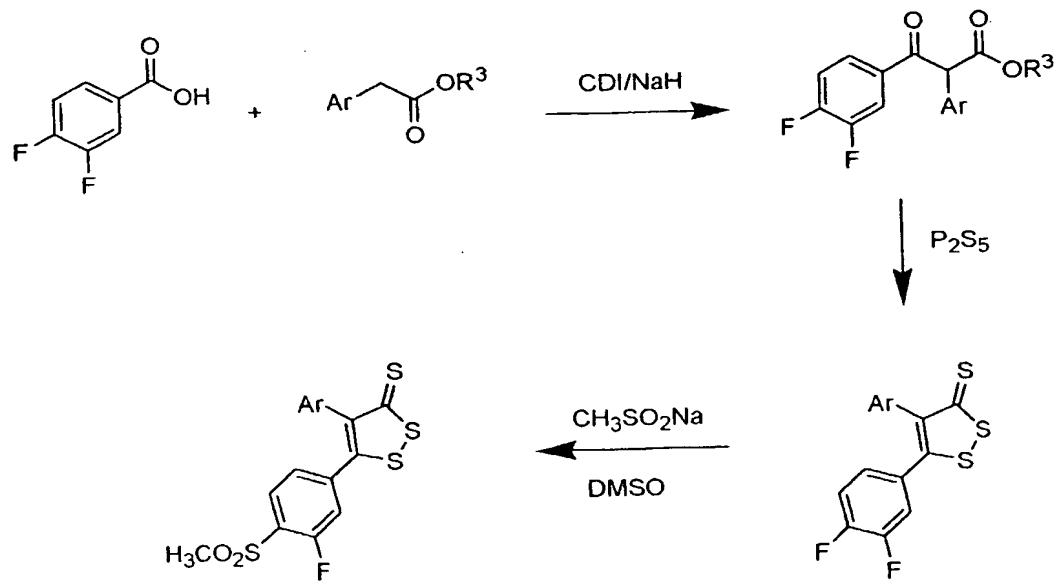
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## Reaction formula 1



wherein, A, B, Ar,  $\text{R}^1$ ,  $\text{R}^2$ , and  $\text{R}^3$  are as defined in the above.

When  $\text{R}^1$  is fluorine in the formula 1a of the present invention, the method for preparing a compound of the present invention may be 5 expressed by the following scheme 2:



wherein, Ar and  $\text{R}^3$  are as defined in the above.

According to another aspect of the present invention, there is 10 provided a pharmaceutical composition comprising a therapeutically

effective amount of a thione derivative of formula 1 or a non-toxic salt thereof as an active ingredient and a pharmaceutically acceptable carrier for treatment of fever, pain, and inflammation.

5 The pharmaceutical composition comprises a compound of formula 1 or a non-toxic salt thereof when it is a selective inhibitor of cyclooxygenase-2. Therefore, the pharmaceutical composition can be used as an antipyretic, an analgesic, and an antiinflammatory agent, with reduced side effects.

10 Conventional nonsteroidal antiinflammatory agents non-selectively inhibit the prostaglandin synthesis enzymes, cyclooxygenase-1 and cyclooxygenase-2. Therefore, various side effects may occur.

15 On the other hand, a compound of formula 1 and a non-toxic salt thereof selectively inhibit cyclooxygenase-2. Therefore, the side effects of conventional nonsteroidal antipyretics, analgesics, and antiinflammatory agents can be reduced.

20 The pharmaceutical composition of the present invention comprises a compound of formula 1 and/or a non-toxic salt thereof and a pharmaceutically acceptable carrier or excipient. Therefore, the pharmaceutical composition may be used as a substitute for conventional nonsteroidal antiinflammatory agents. In particular, due to the reduction of the side effects of conventional nonsteroidal antipyretics, analgesics, and antiinflammatory agents, the pharmaceutical composition of the present invention is useful in treating patients with peptic ulcer, gastritis, regional enteritis, ulcerative colitis, diverticulitis, 25 gastrorrhagia, or hypoprothrombinemia.

30 The pharmaceutical composition of the present invention can be used in all inflammatory diseases associated with pathological prostaglandin and is particularly useful in treating osteoarthritis and rheumatoid arthritis which require high dosage of nonsteroidal antiinflammatory agents.

The pharmaceutical composition of the present invention can be administered in the form of an adult dosage of 1 mg/day to 1000 mg/day of the compound of formula 1. An adequate dosage is determined depending on the degree of disease severity.

35 The pharmaceutical composition of the present invention may be administered in the form of tablet, foam tablet, capsule, granule, powder, sustained-release tablet, sustained-release capsule (a single unit

formulation or a multiple unit formulation), intravenous and intramuscular injectable solution, infusion solution, suspension, or suppository, or in other suitable dosage forms.

5 Sustained-release pharmaceutical dosage forms contain active ingredients with or without an initial loading dose. They are wholly or partially sustained-release pharmaceutical dosage forms to release active ingredients in a controlled manner.

Preferably, the pharmaceutical composition is orally administered.

10 The pharmaceutical composition further comprises a pharmaceutically acceptable excipient and/or diluent and/or adjuvant in pharmaceutically effective amounts.

15 Examples of the excipient and adjuvant include gelatin, a natural sugar such as sucrose and lactose, lecithin, pectin, starch such as corn starch and amylose, cyclodextrin and cyclodextrin derivative, dextran, polyvinylpyrrolidone, polyvinyl acetate, Arabic gum, arginic acid, xylose, talc, salicylic acid, calcium hydrogen phosphate, cellulose, cellulose derivative such as methylcellulose, methoxypropyl cellulose, hydroxypropylmethyl cellulose, and hydroxypropylmethylcellulose phthalate, fatty acid having 12 to 22 carbon atoms, emulsifying agent, oil 20 and fat, in particular, vegetable glycerol ester and polyglycerol ester of saturated fatty acids, monohydric alcohol, polyhydric alcohol, polyglycol such as polyethylene glycol, aliphatic alcohol having 1 to 20 carbon atoms, or aliphatic saturated or unsaturated fatty acid ester having 2 to 22 carbon atoms with polyhydric alcohols such as glycol, glycerol, 25 diethylene glycol, 1,2-propylene glycol, sorbitol, and mannitol.

Other suitable adjuvants include a disintegrating agent. Examples of the disintegrating agent include a cross-linked polyvinylpyrrolidone, sodium carboxymethyl starch, sodium carboxymethyl cellulose, and microcrystalline cellulose. A coating agent 30 which is conventionally used in this field may also be used. Examples of the coating agent include acrylic acid and/or methacrylic acid and/or an ester polymer or copolymer thereof, zein, ethyl cellulose, ethyl cellulose succinate, and Shellac.

35 A plasticizer suitable for the coating agent is citric ester and tartaric ester, glycerol and glycerol ester, or polyethylene glycol with different chain lengths.

A liquid composition such as solution and suspension is formulated in water or a physiological acceptable organic solvent such as alcohol and aliphatic alcohol.

5 The liquid pharmaceutical composition may further comprise a preservative such as potassium solvate, methyl 4-hydroxybenzoate, and propyl 4-hydroxybenzoate, an antioxidant such as ascorbic acid, and a fragrant such as peppermint oil.

10 In addition, when the liquid pharmaceutical composition is formulated, a conventional solubilizer or emulsifier such as polyvinylpyrrolidone and polysolvate 80 may be used.

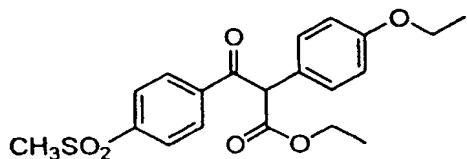
15 Other examples of suitable excipients and adjuvants are disclosed in Dr.H.P. Fielder, "Lexikon der Hilfsstoffe fur Pharmazie, Kosmetik und angrenzende Gebiete" [Encyclopaedia of auxiliaries for pharmacy, cosmetics and related fields].

15 Hereinafter, the present invention will be described more specifically by examples. However, the following examples are provided only for illustration and thus the present invention is not limited to or by them.

Example 1

20 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

Formula 5



25 499 mg of 4-ethoxyphenylacetic acid ethyl ester, 480 mg of carbonyldiimidazole, and 0.5 g of 4-methanesulfonyl benzoic acid were dissolved in 10 ml of dimethyl formamide, and 119 mg of sodium hydride were slowly added dropwise to the solution and the mixture was reacted at the room temperature for 12 hours. Afterwards, water was added to dilute the resultant, followed by extraction with ethyl acetate. The 30 obtained organic layer was dried over anhydrous magnesium sulfate to give 0.9 g of the titled compound as a light yellow liquid(yield 92%).

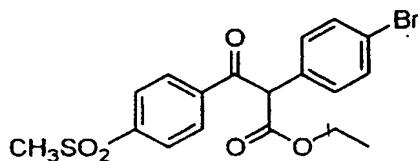
<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ <sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 8.14(d, 2H, J=8.4Hz), 8.04(d, 2H, J=8.4Hz), 6.95(d, 2H, J=8.4Hz), 6.65(d, 2H, J=8.4Hz), 5.56(s, 1H), 4.12(q, 2H, J=6Hz), 3.98(q, 2H, J=6.0Hz), 3.02(s, 3H), 1.33-1.31(m, 6H)

5

Example 2

2-(4-bromophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

Formula 6



10

1.2 g (yield 89%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 700 mg of 4-bromophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

15

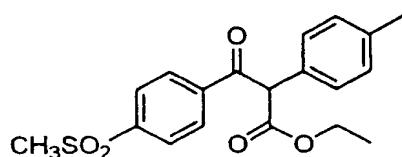
<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 8.15(d, 2H, J=8.4Hz), 8.05(d, 2H, J=8.4Hz), 6.97(d, 2H, J=8.4Hz), 6.94(d, 2H, J=8.4Hz), 5.55(s, 1H), 4.12(q, 2H, J=6Hz), 3.02(s, 3H), 1.33(t, 3H, J=4.0Hz)

20

Example 3

3-(4-methanesulfonyl)-3-oxo-2-p-toryl-propionic acid ethyl ester

Formula 7



25

1.5 g (yield 83%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 890 mg of p-torylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

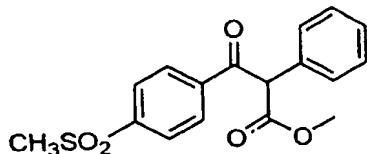
<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 8.14(d, 2H, J=8.4Hz), 8.03(d, 2H,

*J*=8.4Hz), 6.96(d, 2H, *J*=8.4Hz), 6.93(d, 2H, *J*=8.4Hz), 5.56(s, 1H), 4.12(q, 2H, *J*=6Hz), 3.02(s, 3H), 2.33(s, 2H), 1.33(t, 3H, *J*=4.0Hz)

Example 4

5 3-(4-methanesulfonylphenyl)-3-oxo-2-phenylpropionic acid methyl ester

Formula 8



10 1.3 g (yield 80%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 940 mg of phenylacetic acid methyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

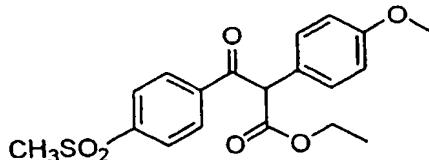
$^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.15(d, 2H, *J*=8.4Hz), 8.05(d, 2H, *J*=8.4Hz), 6.97-6.94(m, 5H), 5.56(s, 1H), 3.75(s, 3H), 3.02(s, 3H)

15

Example 5

3-(4-methanesulfonylphenyl)-2-(4-methoxyphenyl)-3-oxo-propionic acid ethyl ester

Formula 9



20

1.5 g (yield 83%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 970 mg of 4-methoxyphenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

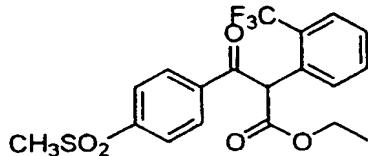
25  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.15(d, 2H, *J*=8.4Hz), 8.05(d, 2H, *J*=8.4Hz), 6.96(d, 2H, *J*=8.4Hz), 6.93(d, 2H, *J*=8.4Hz), 5.56(s, 1H),

4.12(q, 2H,  $J=6.0\text{Hz}$ ), 3.79(s, 3H), 3.02(s, 3H), 1.33(t, 3H,  $J=4.0\text{Hz}$ )

Example 6

5 3-(4-methanesulfonylphenyl)-3-oxo-2-(2-trifluoromethylphenyl)-propionic acid ethyl ester

Formula 10



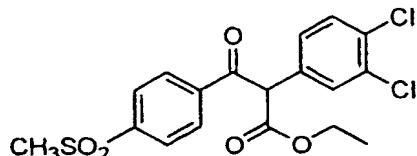
10 0.5 g (yield 65%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 900 mg of 2-trifluoromethylphenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

15  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.14(d, 2H,  $J=8.4\text{Hz}$ ), 8.04(d, 2H,  $J=8.4\text{Hz}$ ), 7.33(d, 1H,  $J=6.8\text{Hz}$ ), 7.14(t, 1H,  $J=6.0\text{Hz}$ ), 7.00-7.68(m, 2H), 5.53(s, 1H), 4.12(q, 2H,  $J=6.0\text{Hz}$ ), 3.02(s, 3H), 1.33(t, 3H,  $J=4.0\text{Hz}$ )

15 Example 7

20 2-(4-chlorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

Formula 11



20

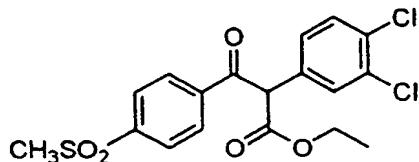
1.5 g (yield 78%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 990 mg of 4-chlorophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

25  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.13(d, 2H,  $J=8.4\text{Hz}$ ), 8.04(d, 2H,  $J=8.4\text{Hz}$ ), 6.96(d, 2H,  $J=8.4\text{Hz}$ ), 6.92(d, 2H,  $J=8.4\text{Hz}$ ), 5.55(s, 1H), 4.12(q, 2H,  $J=6.0\text{Hz}$ ), 3.02(s, 3H), 1.33(t, 3H,  $J=4.0\text{Hz}$ )

Example 8

2-(3,4-dichlorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

5 Formula 12



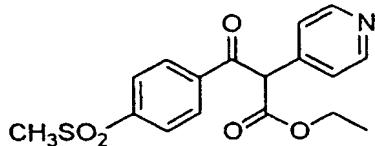
10 1.7 g (yield 85%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 990 mg of 3,4-dichlorophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 8.14(d, 2H, J=8.4Hz), 8.04(d, 2H, J=8.4Hz), 7.09(d, 1H, J=6.8Hz), 7.01(s, 1H), 6.88(d, 1H, J=6.8Hz), 5.53(s, 1H), 4.12(q, 2H, J=6.0Hz), 3.02(s, 3H), 1.33(t, 3H, J=4.0Hz)

15 Example 9

3-(4-methanesulfonylphenyl)-3-oxo-2-(pyridine-4-yl)-propionic acid ethyl ester

Formula 13



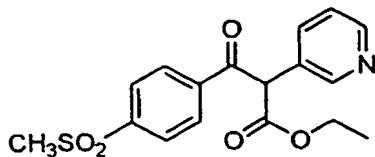
20 1.5 g (yield 78%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 800 mg of pyridine-4-yl-acetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

25 <sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 8.55(d, 2H, J=4.00Hz), 7.85(d, 2H, J=9.2Hz), 7.39(d, 2H, J=9.2Hz), 6.99(d, 2H, J=4.0Hz), 5.50(s, 1H), 4.12(q, 2H, J=6.0Hz), 3.02(s, 3H), 1.33(t, 3H, J=4.0Hz)

Example 10

3-(4-methanesulfonylphenyl)-3-oxo-2-(pyridine-3-yl)-propionic acid ethyl ester

5      Formula 14



1.35 g (yield 78%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 1 g of pyridien-3-yl-acetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

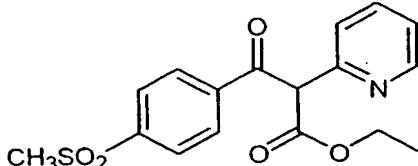
10       $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.56(s, 1H), 8.24(d, 1H,  $J=4.0\text{Hz}$ ), 7.92(d, 2H,  $J=8.0\text{Hz}$ ), 7.54(d, 1H,  $J=4.0\text{Hz}$ ), 7.45(d, 2H,  $J=8.0\text{Hz}$ ), 7.32(t, 1H,  $J=6.0\text{Hz}$ ), 5.50(s, 1H), 4.12(q, 2H,  $J=6.0\text{Hz}$ ), 3.03(s, 3H), 1.33(t, 3H,  $J=4.0\text{Hz}$ )

15

Example 11

3-(4-methanesulfonylphenyl)-3-oxo-2-(pyridine-2-yl)-propionic acid ethyl ester

Formula 15



20

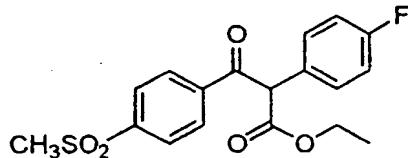
1.35 g (yield 78%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 1 g of pyridine-2-yl-acetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

25       $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.56(d, 1H,  $J=6.8\text{Hz}$ ), 8.14(d, 2H,  $J=8.4\text{Hz}$ ), 8.04(d, 2H,  $J=8.4\text{Hz}$ ), 7.27-7.22(m, 3H), 5.56(s, 1H), 4.12(q, 2H,  $J=6.0\text{Hz}$ ), 3.14(s, 3H), 1.37(t, 3H,  $J=4.0\text{Hz}$ )

Example 12

2-(4-fluorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

5                   Formula 16



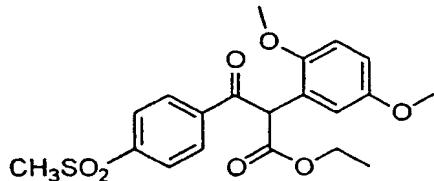
10                  1.54 g (yield 85%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 1 g of 4-fluorophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

15                  <sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 8.13(d, 2H, J=8.4Hz), 8.04(d, 2H, J=8.4Hz), 7.09-7.04(m, 4H), 5.55(s, 1H), 4.12(q, 2H, J=6.0Hz), 3.02(s, 3H), 1.33(t, 3H, J=4.0Hz)

15                  Example 13

20                  2-(2,5-dimethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

                        Formula 17



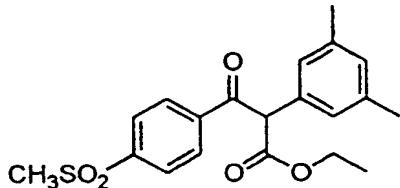
20                  0.9 g (yield 90%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 560 mg of 2,5-dimethoxyphenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

25                  <sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 8.13(d, 2H, J=8.4Hz), 8.04(d, 2H, J=8.4Hz), 6.96(d, 2H, J=8.4Hz), 6.92(d, 2H, J=8.4Hz), 5.55(s, 1H), 4.12(q, 2H, J=6.0Hz), 3.02(s, 3H), 1.33(t, 3H, J=4.0Hz)

### Example 14

**2-(3,5-dimethylphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester**

## 5 Formula 18



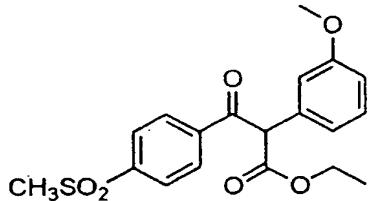
810 mg (yield 88%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 460 mg of 3,5-dimethylphenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 8.13(d, 2H, J=8.4Hz), 8.04(d, 2H, J=8.4Hz), 6.96(d, 2H, J=8.4Hz), 6.92(d, 2H, J=8.4Hz), 5.55(s, 1H), 4.12(q, 2H, J=6.0Hz), 3.02(s, 3H), 2.32(s, 6H), 1.33(t, 3H, J=4.0Hz)

### 15 Example 15

## 3-(4-methanesulfonylphenyl)-2-(3-methoxyphenyl)-3-oxo-propionic acid ethyl ester

### Formula 19



20 860 mg (yield 92%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 460 mg of 3-methoxyphenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

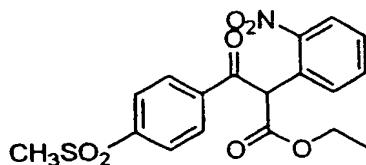
<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 8.13(d, 2H, *J*=8.4Hz), 8.04(d, 2H, *J*=8.4Hz), 7.03(t, 1H, *J*=4.2Hz), 6.57-6.58(m, 3H), 5.55(s, 1H), 4.12(q,

2H,  $J=6.0\text{Hz}$ ), 3.72(s, 3H), 3.02(s, 3H), 1.33(t, 3H,  $J=4.0\text{Hz}$ )

Example 16

5       3-(4-methanesulfonylphenyl)-2-(2-nitrophenyl)-3-oxo-propionic acid ethyl ester

Formula 20



10       830 mg (yield 85%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 500 mg of 2-nitrophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

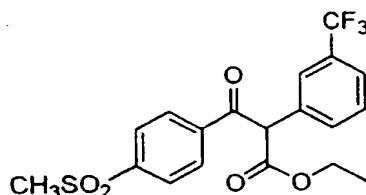
15        $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.13(d, 2H,  $J=8.4\text{Hz}$ ), 8.07(d, 1H,  $J=6.4\text{Hz}$ ), 8.04(t, 1H,  $J=4.2\text{Hz}$ ), 7.53-7.52(m, 1H), 7.33-7.32(m, 2H), 5.55(s, 1H), 4.12(q, 2H,  $J=6.0\text{Hz}$ ), 3.02(s, 3H), 1.33(t, 3H,  $J=4.0\text{Hz}$ )

15

Example 17

20       3-(4-methanesulfonylphenyl)-3-oxo-2-(3-trifluoromethylphenyl)-propanoic acid ethyl ester

Formula 21



20

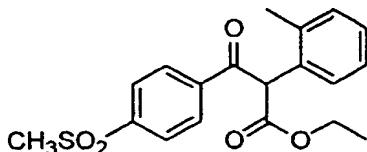
25       830 mg (yield 85%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 500 mg of 3-trifluoromethylphenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

25        $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.13(d, 2H,  $J=8.4\text{Hz}$ ), 8.04(d, 2H,  $J=8.4\text{Hz}$ ), 7.26-7.06(m, 2H), 5.55(s, 1H), 4.12(q, 2H,  $J=6.0\text{Hz}$ ), 3.72(s, 3H), 3.02(s, 3H), 1.33(t, 3H,  $J=4.0\text{Hz}$ )

Example 18

3-(4-methanesulfonylphenyl)-3-oxo-2-o-toryl-propionic acid ethyl ester

5                   Formula 22



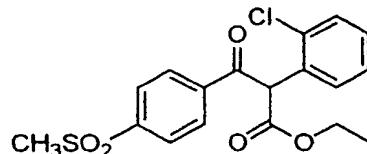
820 mg (yield 91%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 420 mg of o-torylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

10                   <sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 8.13(d, 2H, J=8.4Hz), 8.04(d, 2H, J=8.4Hz), 6.95-6.93(m, 4H), 5.55(s, 1H), 4.12(q, 2H, J=6.0Hz), 3.02(s, 3H), 2.35(s, 3H), 1.33(t, 3H, J=4.0Hz)

15                   Example 19

2-(2-chlorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

Formula 23

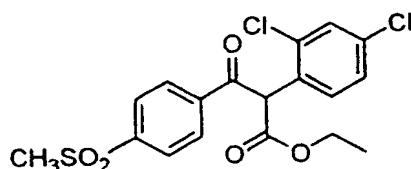


20                   880 mg (yield 93%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 490 mg of 2-chlorophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

25                   <sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 8.13(d, 2H, J=8.4Hz), 8.04(d, 2H, J=8.4Hz), 6.97-6.98(m, 4H), 5.55(s, 1H), 4.12(q, 2H, J=6.0Hz), 3.02(s, 3H), 1.33(t, 3H, J=4.0Hz)

Example 20

2-(2,4-dichlorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester  
Formula 24



5

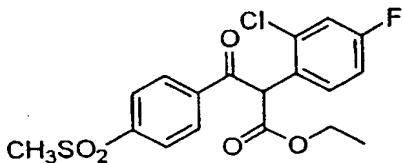
800 mg (yield 85%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 470 mg of 2,4-dichlorophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

10  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.13(d, 2H,  $J=8.4\text{Hz}$ ), 8.04(d, 2H,  $J=8.4\text{Hz}$ ), 7.16(s, 1H), 7.03-7.01(m, 2H), 5.55(s, 1H), 4.12(q, 2H,  $J=6.0\text{Hz}$ ), 3.02(s, 3H), 1.33(t, 3H,  $J=4.0\text{Hz}$ )

Example 21

15 2-(2-chloro-4-fluorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

Formula 25



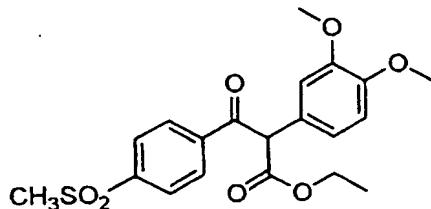
20 836 mg (yield 88%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 520 mg of 2-chloro-4-fluorophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

25  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.13(d, 2H,  $J=8.4\text{Hz}$ ), 8.04(d, 2H,  $J=8.4\text{Hz}$ ), 6.98(t, 1H,  $J=6.0\text{Hz}$ ), 6.86(d, 1H,  $J=5.6\text{Hz}$ ), 6.73(d, 1H,  $J=5.6\text{Hz}$ ), 5.55(s, 1H), 4.12(q, 2H,  $J=6.0\text{Hz}$ ), 3.02(s, 3H), 1.33(t, 3H,  $J=4.0\text{Hz}$ )

Example 22

2-(3,4-dimethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

## Formula 26



5

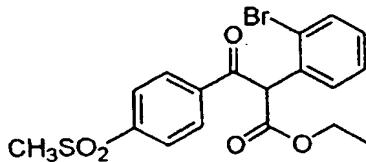
760 mg (yield 80%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 560 mg of 3,4-dimethoxyphenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

10  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.13(d, 2H,  $J=8.4\text{Hz}$ ), 8.04(d, 2H,  $J=8.4\text{Hz}$ ), 6.53-6.51(m, 2H), 6.46(s, 1H), 5.55(s, 1H), 4.12(q, 2H,  $J=6.0\text{Hz}$ ), 3.73(s, 6H), 3.02(s, 3H), 1.33(t, 3H,  $J=4.0\text{Hz}$ )

Example 23

15 2-(2-bromophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

## Formula 27



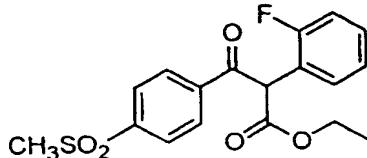
20 900 mg (yield 85%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 660 mg of 2-bromophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

25  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.13(d, 2H,  $J=8.4\text{Hz}$ ), 8.04(d, 2H,  $J=8.4\text{Hz}$ ), 6.99-6.97(m, 4H), 5.55(s, 1H), 4.12(q, 2H,  $J=6.0\text{Hz}$ ), 3.02(s, 3H), 1.33(t, 3H,  $J=4.0\text{Hz}$ )

Example 24

2-(2-fluorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

Formula 28



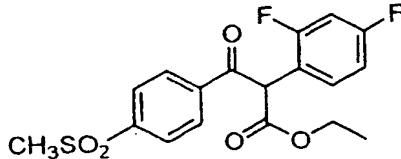
800 mg (yield 88%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 440 mg of 2-fluorophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

10  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.13(d, 2H,  $J=8.4\text{Hz}$ ), 8.04(d, 2H,  $J=8.4\text{Hz}$ ), 7.03-7.01(m, 4H), 5.55(s, 1H), 4.12(q, 2H,  $J=6.0\text{Hz}$ ), 3.02(s, 3H), 1.33(t, 3H,  $J=4.0\text{Hz}$ )

Example 25

15 2-(2,4-difluorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

Formula 29



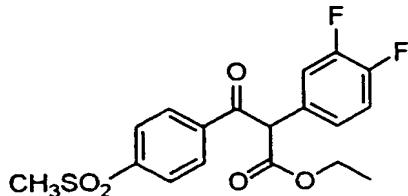
849 mg (yield 89%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 480 mg of 2,4-difluorophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

20  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.13(d, 2H,  $J=8.4\text{Hz}$ ), 8.04(d, 2H,  $J=8.4\text{Hz}$ ), 7.02-7.01(m, 2H), 6.56(m, 1H), 5.55(s, 1H), 4.12(q, 2H,  $J=6.0\text{Hz}$ ), 3.02(s, 3H), 1.33(t, 3H,  $J=4.0\text{Hz}$ )

Example 26

2-(3,4-difluorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic

c acid ethyl ester  
Formula 30



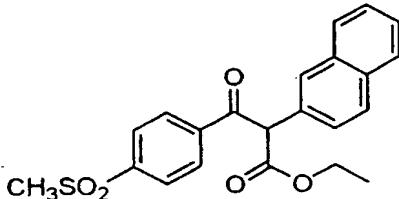
874 mg (yield 92%) of the titled compound as a liquid was  
5 prepared in the same manner as in Example 1 except using 480 mg of  
3,4-difluorophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic  
acid ethyl ester.

10  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.13(d, 2H,  $J=8.4\text{Hz}$ ), 8.04(d, 2H,  
 $J=8.4\text{Hz}$ ), 6.83-6.81(m, 2H), 6.75(m, 1H), 5.55(s, 1H), 4.12(q, 2H,  
 $J=6.0\text{Hz}$ ), 3.02(s, 3H), 1.33(t, 3H,  $J=4.0\text{Hz}$ )

Example 27

3-(4-methanesulfonylphenyl)-2-(naphthalene-2-yl)-3-oxo-propionic  
acid ethyl ester

15 Formula 31



870 mg (yield 88%) of the titled compound as a liquid was  
prepared in the same manner as in Example 1 except using 530 mg of  
naphthalene-2-yl-acetic acid ethyl ester instead of 4-ethoxyphenylacetic  
acid ethyl ester.

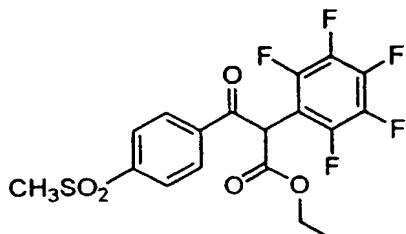
20  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.13(d, 2H,  $J=8.4\text{Hz}$ ), 8.04(d, 2H,  
 $J=8.4\text{Hz}$ ), 7.68-7.64(m, 3H), 7.46(s, 1H), 7.31-7.30(m, 2H), 7.16-7.15(m,  
1H), 5.55(s, 1H), 4.12(q, 2H,  $J=6.0\text{Hz}$ ), 3.02(s, 3H), 1.33(t, 3H,  
 $J=4.0\text{Hz}$ )

25

Example 28

3-(4-methanesulfonylphenyl)-3-oxo-2-pentafluorophenyl-propionic acid ethyl ester

Formula 32



5

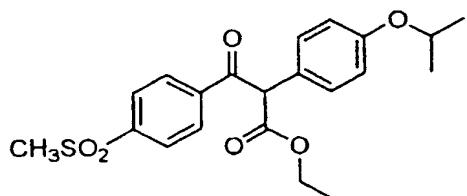
880 mg (yield 85%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 550 mg of pentafluorophenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

10  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.13(d, 2H,  $J=8.4\text{Hz}$ ), 8.04(d, 2H,  $J=8.4\text{Hz}$ ), 5.53(s, 1H), 4.12(q, 2H,  $J=6.0\text{Hz}$ ), 3.01(s, 3H), 1.33(t, 3H,  $J=4.0\text{Hz}$ )

Example 29

15 2-(4-isopropoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

Formula 33



20 860 mg (yield 88%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 500 mg of 4-isopropoxyphenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

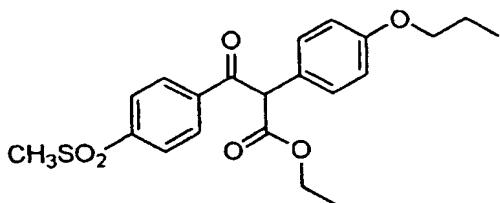
25  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.14(d, 2H,  $J=8.4\text{Hz}$ ), 8.04(d, 2H,  $J=8.4\text{Hz}$ ), 6.95(d, 2H,  $J=8.4\text{Hz}$ ), 6.65(d, 2H,  $J=8.4\text{Hz}$ ), 5.56(s, 1H), 4.12(q, 2H,  $J=6\text{Hz}$ ), 4.04-4.02(m, 1H), 3.02(s, 3H), 1.38(s, 3H), 1.37(s,

3H), 1.31(t, 3H,  $J=4.0\text{Hz}$ )

Example 30

5       3-(4-methanesulfonylphenyl)-3-oxo-2-(4-propoxyphenyl)-propionic acid ethyl ester

Formula 34



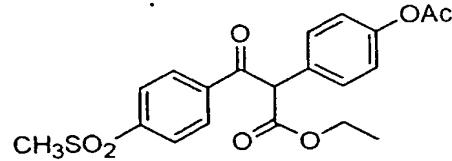
10       890 mg (yield 92%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 500 mg of 4-propoxyphenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

15        $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.14(d, 2H,  $J=8.4\text{Hz}$ ), 8.04(d, 2H,  $J=8.4\text{Hz}$ ), 6.95(d, 2H,  $J=8.4\text{Hz}$ ), 6.65(d, 2H,  $J=8.4\text{Hz}$ ), 5.56(s, 1H), 4.12(q, 2H,  $J=6\text{Hz}$ ), 3.94-3.95(m, 2H), 3.02(s, 3H), 1.75-1.74(m, 2H), 1.30-1.28(m, 6H)

Example 31

20       2-(4-acetoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

Formula 35



25       848 mg (yield 84%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 500 mg of 4-acetoxyphenylacetic acid ethyl ester instead of 4-ethoxyphenylacetic acid ethyl ester.

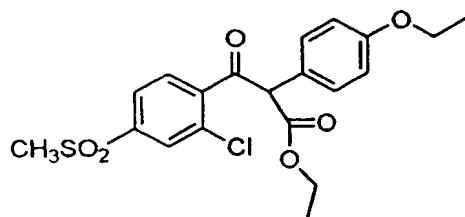
1        $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.14(d, 2H,  $J=8.4\text{Hz}$ ), 8.04(d, 2H,  $J=8.4\text{Hz}$ ), 7.03(d, 2H,  $J=8.4\text{Hz}$ ), 6.95(d, 2H,  $J=8.4\text{Hz}$ ), 5.56(s, 1h), 4.12(q,

2H,  $J=6.0\text{Hz}$ ), 3.12(s, 3H), 2.08(s, 3H), 1.30(t, 3H,  $J=4.0\text{Hz}$ )

Example 32

5 3-(2-chloro-4-methanesulfonylphenyl)-2-(4-ethoxyphenyl)-3-oxo-propionic acid ethyl ester

Formula 36



10 670 mg (yield 75%) of the titled compound as a liquid was prepared in the same manner as in Example 1 except using 500 mg of 2-chloro-4-methanesulfonylbenzoic acid instead of 4-methanesulfonylbenzoic acid.

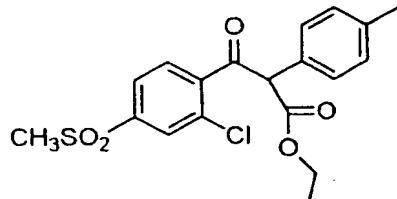
15  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.08(d, 1H,  $J=7.2\text{Hz}$ ), 8.05(s, 1H), 7.92(d, 1H,  $J=7.2\text{Hz}$ ), 6.95-6.94(m, 4H), 5.56(s, 1H), 4.12(q, 2H,  $J=6\text{Hz}$ ), 3.98(q, 2H,  $J=6.0\text{Hz}$ ), 3.02(s, 3H), 1.33-1.31(m, 6H)

20

Example 33

3-(2-chloro-4-methanesulfonylphenyl)-3-oxo-2-p-toryl-propionic acid ethyl ester

Formula 37



25

740 mg (yield 88%) of the titled compound as a liquid was prepared in the same manner as in Example 3 except using 500 mg of 2-chloro-4-methanesulfonylbenzoic acid instead of 4-methanesulfonylbenzoic acid.

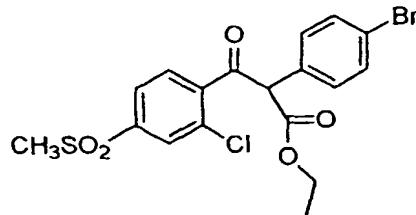
25  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.08(d, 1H,  $J=7.2\text{Hz}$ ), 8.05(s, 1H),

7.92(d, 1H,  $J=7.2\text{Hz}$ ), 6.95-6.94(m, 4H), 5.56(s, 1H), 4.12(q, 2H,  $J=6\text{Hz}$ ),  
3.02(s, 3H), 2.35(s, 3H), 1.33(t, 3H,  $J=4.0\text{Hz}$ )

Example 34

5 2-(4-bromophenyl)-3-(2-chloro-4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester

Formula 38



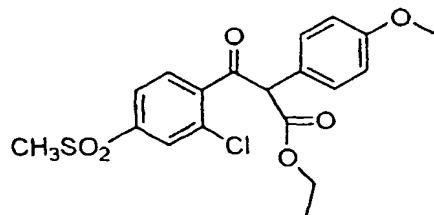
10 764 mg (yield 84%) of the titled compound as a liquid was prepared in the same manner as in Example 2 except using 500 mg of 2-chloro-4-methanesulfonylbenzoic acid instead of 4-methanesulfonylbenzoic acid.

15  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.08(d, 1H,  $J=7.2\text{Hz}$ ), 8.05(s, 1H), 7.92(d, 1H,  $J=7.2\text{Hz}$ ), 6.98-6.97(m, 4H), 5.55(s, 1H), 4.13(q, 2H,  $J=6\text{Hz}$ ), 3.02(s, 3H), 1.33(t, 3H,  $J=4.0\text{Hz}$ )

Example 35

20 3-(2-chloro-4-methanesulfonylphenyl)-2-(4-methoxyphenyl)-3-oxo-propionic acid ethyl ester

Formula 39



25 791 mg (yield 87%) of the titled compound as a liquid was prepared in the same manner as in Example 5 except using 500 mg of 2-chloro-4-methanesulfonylbenzoic acid instead of 4-methanesulfonylbenzoic acid.

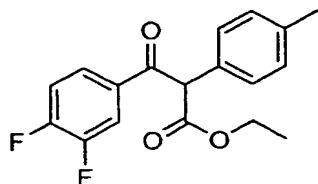
$^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  8.08(d, 1H,  $J=7.2\text{Hz}$ ), 8.05(s, 1H),

7.92(d, 1H,  $J=7.2\text{Hz}$ ), 6.95-6.94(m, 4H), 5.56(s, 1H), 4.13(q, 2H,  $J=6\text{Hz}$ ),  
3.75(s, 3H), 3.02(s, 3H), 1.33(t, 3H,  $J=4.0\text{Hz}$ )

Example 36

5 3-(3,4-difluorophenyl)-3-oxo-2-p-toryl-propionic acid ethyl ester

Formula 40



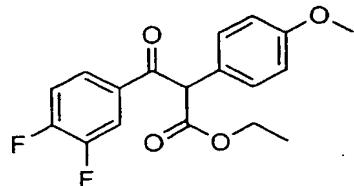
10 1.73 g (yield 82%) of the titled compound as a liquid was prepared in the same manner as in Example 3 except using 1 g of 3,4-difluorobenzoic acid instead of 4-methanesulfonylbenzoic acid.

15  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  7.17(d, 2H,  $J=7.6\text{Hz}$ ), 7.05-7.03(m, 3H), 6.99(d, 2H,  $J=7.6\text{Hz}$ ), 5.52(s, 1H), 4.12(q, 2H,  $J=6.0\text{Hz}$ ), 2.35(s, 3H), 1.30(t, 3H,  $J=4.0\text{Hz}$ )

15 Example 37

3-(3,4-difluorophenyl)-2-(4-methoxyphenyl)-3-oxo-propionic acid ethyl ester

Formula 41



20 850 mg (yield 85%) of the titled compound as a liquid was prepared in the same manner as in Example 5 except using 500 mg of 3,4-difluorobenzoic acid instead of 4-methanesulfonylbenzoic acid.

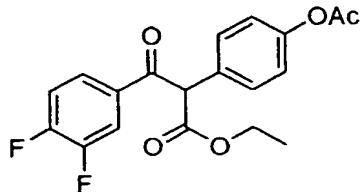
25  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  7.16(d, 2H,  $J=7.6\text{Hz}$ ), 7.04-7.02(m, 3H), 6.99(d, 2H,  $J=7.6\text{Hz}$ ), 5.52(s, 1H), 4.12(q, 2H,  $J=6.0\text{Hz}$ ), 3.82(s, 3H), 1.30(t, 3H,  $J=4.0\text{Hz}$ )

Example 38

2-(4-acetoxyphenyl)-3-(3,4-difluorophenyl)-3-oxo-propionic acid

ethyl ester

Formula 42



830 mg (yield 87%) of the titled compound as a liquid was  
 5 prepared in the same manner as in Example 31 except using 416 mg of  
 3,4-difluorobenzoic acid instead of 4-methanesulfonylbenzoic acid.

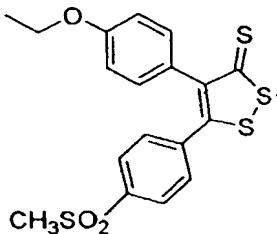
<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 7.17(d, 2H, J=7.6Hz), 7.05-7.03(m,  
 3H), 6.99(d, 2H, J=7.6Hz), 5.52(s, 1H), 4.12(q, 2H, J=6.0Hz), 2.32(s, 3H),  
 1.30(t, 3H, J=4.0Hz)

10

Example 39

4-(4-ethoxyphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thio  
 ne

Formula 43



15

0.68 g of phosphorus pentasulfide was dissolved in 10 ml of  
 toluene, and then 0.3 g of  
 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid  
 ethyl ester was added thereto to reflux for 4 hours at 110°C. Afterwards  
 20 the reaction apparatus was cooled, and ammonia water was added  
 thereto slowly to adjust pH 8 to 8.5. The reaction mixture was diluted  
 with water and extracted with ethyl acetate. The obtained organic layer  
 was dried on anhydrous magnesium sulfate to distill the solvent. The  
 resultant was recrystallized with n-hexane to give 180mg of the titled  
 25 compound as a red solid(yield 60%).

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 7.88(d, 2H, J=8.4Hz), 7.45(d, 2H,

*J*=8.4Hz), 7.01(d, 2H, *J*=6.8Hz), 6.85(d, 2H, *J*=6.8Hz), 4.02(q, 2H, *J*=6.8Hz), 3.05(s, 3H), 1.42(t, 3H, *J*=4.0Hz)

El Mass(M<sup>+</sup>) : 408

Melting point: 210-212°C

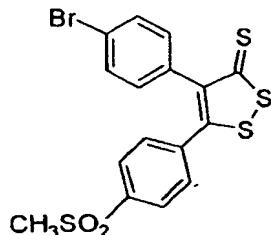
5

Example 40

4-(4-bromophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thio

ne

Formula 44



10

210 mg (yield 68%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(4-bromophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

15 <sup>1</sup>H-NMR(300MHz, CDCl<sub>3</sub>) δ 7.91(d, 2H, *J*=8.4Hz), 7.47(d, 2H, *J*=8.4Hz), 7.45(d, 2H, *J*=8.4Hz), 7.19(d, 2H, *J*=8.4Hz), 3.05(s, 3H)

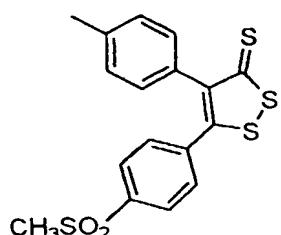
El Mass(M<sup>+</sup>) : 443

20 Melting point: 238-240°C

Example 41

5-(4-methanesulfonylphenyl)-4-p-toryl-[1,2]dithiol-3-thione

Formula 45



25

200 mg (yield 65%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-3-oxo-2-p-toryl-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-5 propionic acid ethyl ester.

10  $^1\text{H-NMR}$ (300MHz,  $\text{CDCl}_3$ )  $\delta$  7.89(d, 2H,  $J=9.0\text{Hz}$ ), 7.46(d, 2H,  $J=9.0\text{Hz}$ ), 7.16(d, 2H,  $J=9.0\text{Hz}$ ), 6.99(d, 2H,  $J=9.0\text{Hz}$ ), 3.05(s, 3H), 2.34(s, 3H)

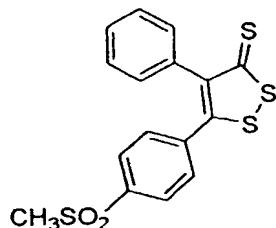
El Mass(M<sup>+</sup>) : 378

15 Melting point: 240-242°C

Example 42

5-(4-methanesulfonylphenyl)-4-phenyl-[1,2]dithiol-3-thione

Formula 46



15

160 mg (yield 50%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-3-oxo-2-phenyl-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-20 propionic acid ethyl ester.

25  $^1\text{H-NMR}$ (300MHz,  $\text{CDCl}_3$ )  $\delta$  7.87(d, 2H,  $J=6.0\text{Hz}$ ), 7.44(d, 2H,  $J=6.0\text{Hz}$ ), 7.35(t, 3H,  $J=4.0\text{Hz}$ ), 7.12-7.10(m, 2H), 3.04(s, 3H)

El Mass(M<sup>+</sup>) : 364

Melting point: 200-202°C

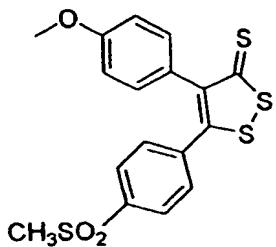
25

Example 43

5-(4-methanesulfonylphenyl)-4-(4-methoxyphenyl)-[1,2]dithiol-3-thi

one

Formula 47



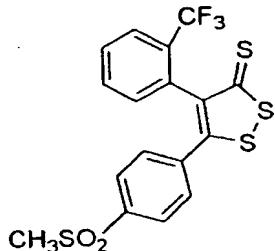
120 mg (yield 40%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-2-(4-methoxyphenyl)-3-oxo-propionic acid 5 ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

10  $^1\text{H-NMR}$ (300MHz,  $\text{CDCl}_3$ )  $\delta$  7.90(d, 2H,  $J=9.0\text{Hz}$ ), 7.46(d, 2H,  $J=9.0\text{Hz}$ ), 7.04(d, 2H,  $J=6.0\text{Hz}$ ), 6.88(d, 2H,  $J=6.0\text{Hz}$ ), 3.81(s, 3H), 3.05(s, 3H)  
 EI Mass( $\text{M}^+$ ) : 394  
 Melting point: 220-222°C

Example 44

15 5-(4-methanesulfonylphenyl)-4-(2-trifluoromethylphenyl)-[1,2]dithio  
 I-3-thione

Formula 48



160 mg (yield 51%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-3-oxo-2-(2-trifluoromethylphenyl)-propionic acid 20 ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

<sup>1</sup>H-NMR(300MHz, CDCl<sub>3</sub>) δ 7.92(d, 2H, J=6.0Hz), 7.63(d, 2H, J=6.0Hz), 7.46(d, 1H, J=9.0Hz), 7.35(d, 1H, J=9.0Hz), 7.24-7.21(m, 2H), 3.05(s, 3H)

FAB Mass(M+1) : 433

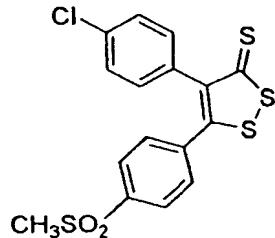
5 Melting point: 240-242°C

Example 45

4-(4-chlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thion

e

10 Formula 49



15 180 mg (yield 45%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.4 g of 2-(4-chlorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

20 <sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 7.93(d, 2H, J=8.0Hz), 7.47(d, 2H, J=8.0Hz), 7.35(d, 2H, J=8.0Hz), 7.07(d, 2H, J=8.0Hz), 2.98(s, 3H)

25 EI Mass(M<sup>+</sup>) : 399

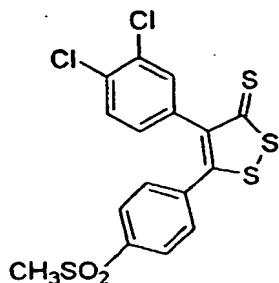
Melting point: 233-235°C

Example 46

4-(3,4-dichlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-t

25 hione

Formula 50



200 mg (yield 48%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.4 g of 2-(3,4-dichlorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

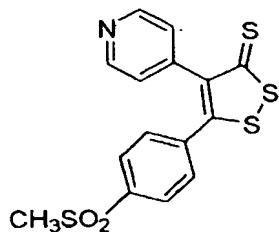
<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 7.98(d, 2H, J=8.0Hz), 7.49(d, 2H, J=8.0Hz), 7.44(d, 1H, J=8.0Hz), 7.35(s, 1H), 7.07(d, 1H, J=8.0Hz), 3.09(s, 3H)

EI Mass(M<sup>+</sup>) : 443

Example 47

5-(4-methanesulfonylphenyl)-4-(pyridine-4-yl)-[1,2]dithiol-3-thione

Formula 51



180 mg (yield 60%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-3-oxo-2-(pyridine-4-yl)-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

<sup>1</sup>H-NMR(300MHz, CDCl<sub>3</sub>) δ 8.55(d, 2H, J=4.0Hz), 7.85(d, 2H,

*J*=9.2Hz), 7.39(d, 2H, *J*=9.2Hz), 6.99(d, 2H, *J*=4.0Hz), 2.98(s, 3H)

El Mass(M<sup>+</sup>) : 365

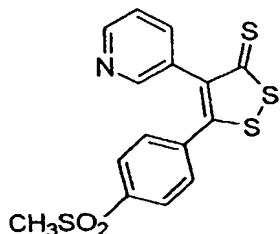
Melting point: 245-247 °C

5

Example 48

5-(4-methanesulfonylphenyl)-4-(pyridine-3-yl)-[1,2]dithiol-3-thione

Formula 52



10 189 mg (yield 61%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-3-oxo-2-(pyridine-3-yl)-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

15 <sup>1</sup>H-NMR(300MHz, CDCl<sub>3</sub>) δ 8.58(s, 1H), 8.25(d, 2H, *J*=4.0Hz), 7.92(d, 2H, *J*=8.0Hz), 7.54(d, 1H, *J*=4.0Hz), 7.45(d, 2H, *J*=8.0Hz), 3.03(s, 3H)

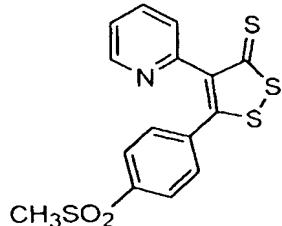
El Mass(M<sup>+</sup>) : 365

20

Example 49

5-(4-methanesulfonylphenyl)-4-(pyridine-2-yl)-[1,2]dithiol-3-thione

Formula 53



189 mg (yield 61%) of the titled compound as a liquid was

prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-3-oxo-2-(pyridine-2-yl)-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

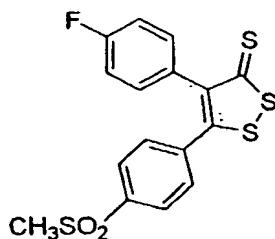
<sup>1</sup>H-NMR(300MHz, CDCl<sub>3</sub>) δ 8.55(m, 1H), 7.87(dt, 2H, J=8.6Hz, J=2.1Hz), 7.75(ddd, 1H, J=9.5Hz, J=2.1Hz, J=1.8Hz), 7.50(dt, 2H, J=8.6Hz, J=2.1Hz), 7.40(dt, 1H, J=7.9Hz, J=1.0Hz), 7.26(ddd, 1H, J=7.6Hz, J=5.1Hz, J=1.7Hz), 3.04(s, 3H)

10 EI Mass(M<sup>+</sup>) : 365

Example 50

4-(4-fluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thion

e  
15 Formula 54



195 mg (yield 63%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(4-fluorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

<sup>1</sup>H-NMR(300MHz, CDCl<sub>3</sub>) δ 7.90(d, 2H, J=8.0Hz), 7.44(d, 2H, J=8.0Hz), 7.09-7.04(m, 4H), 3.05(s, 3H)

25 EI Mass(M<sup>+</sup>) : 382

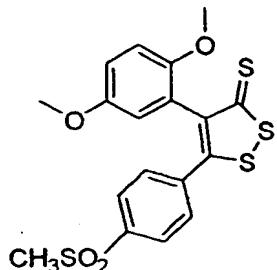
Melting point: 195-197 °C

Example 51

4-(2,5-dimethoxyphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-

## 3-thione

Formula 55



180 mg (yield 60%) of the titled compound as a liquid was  
 5 prepared in the same manner as in Example 39 except using 0.3 g of  
 2-(2,5-dimethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic  
 acid ethyl ester instead of  
 10 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid  
 ethyl ester.

15  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  7.87(d, 2H,  $J=8.4\text{Hz}$ ), 7.51(d, 2H,  
 $J=8.4\text{Hz}$ ), 6.87(dd, 1H,  $J=12.0\text{Hz}$ ,  $J=2.8\text{Hz}$ ), 6.78(d, 1H,  $J=12\text{Hz}$ ), 6.62(d,  
 1H,  $J=2.8\text{Hz}$ ), 3.72(s, 3H), 3.53(s, 3H), 3.03(s, 3H)

El Mass(M $^+$ ) : 424

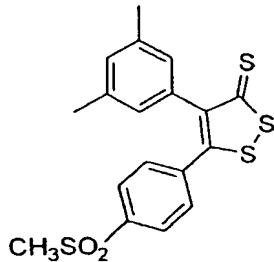
Melting point: 176-177 °C

15

Example 52

4-(3,5-dimethylphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione

Formula 56



20

210 mg (yield 66%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(3,5-dimethylphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid

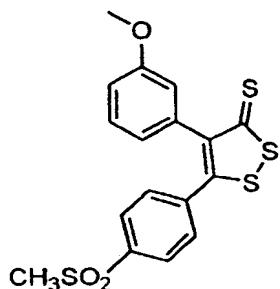
ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

15  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  7.88(d, 2H,  $J=8.4\text{Hz}$ ), 7.47(d, 2H,  $J=8.4\text{Hz}$ ), 6.96(s, 1H), 6.69(s, 2H), 3.03(s, 3H), 2.37(s, 6H)  
 20 EI Mass( $M^+$ ) : 392  
 Melting point: 164-165  $^\circ\text{C}$

Example 53

10 5-(4-methanesulfonylphenyl)-4-(3-methoxyphenyl)-[1,2]dithiol-3-thione

Formula 57



15 210 mg (yield 66%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-2-(3-methoxyphenyl)-3-oxo-propionic acid instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

20  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  7.89(d, 2H,  $J=8.4\text{Hz}$ ), 7.49(d, 2H,  $J=8.4\text{Hz}$ ), 7.24(t, 1H,  $J=8.2\text{Hz}$ ), 6.88(d, 1H,  $J=7.2\text{Hz}$ ), 6.69(s, 1H), 6.65(d, 1H,  $J=7.2\text{Hz}$ ), 3.71(s, 3H), 3.04(s, 3H)

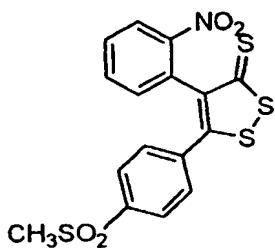
EI Mass( $M^+$ ) : 394

Melting point: 212-213  $^\circ\text{C}$

25

Example 54

5-(4-methanesulfonylphenyl)-4-(2-nitrophenyl)-[1,2]dithiol-3-thione  
 Formula 58



217 mg (yield 70%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-2-(2-nitrophenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 8.13(d, 1H, J=6.8Hz), 7.89(d, 2H, J=8.4Hz), 7.56-7.54(m, 4H), 7.01(d, 1H, J=6.8Hz), 3.04(s, 3H)

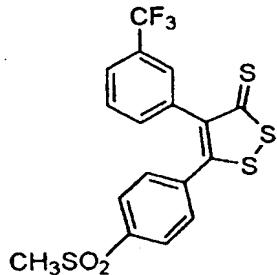
10 EI Mass(M<sup>+</sup>) : 409

Melting point: 170-171 °C

Example 55

15 5-(4-methanesulfonylphenyl)-4-(3-trifluoromethylphenyl)-[1,2]dithio 1-3-thione

Formula 59



240 mg (yield 78%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-3-oxo-2-(3-trifluoromethylphenyl)-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 7.90(d, 2H, J=8.4Hz), 7.59(d, 1H, J=7.6Hz), 7.49(t, 1H, J=8.0Hz), 7.43(d, 2H, J=8.4Hz), 7.38(d, 1H, J=7.6Hz), 7.29(s, 1H), 3.04(s, 3H)

El Mass(M<sup>+</sup>) : 432

5 Melting point: 188-189°C

Example 56

5-(4-methanesulfonylphenyl)-4-o-toryl-[1,2]dithiol-3-thione

Formula 60



10

173 mg (yield 56%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-3-oxo-2-o-toryl-propionic acid ethyl ester instead

15 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

16 <sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 7.87(d, 2H, J=8.4Hz), 7.46(d, 2H, J=8.4Hz), 7.30(d, 1H, J=7.6Hz), 7.22-7.17(m, 2H), 6.96(d, 1H, J=7.6Hz), 3.04(s, 3H), 2.10(s, 3H)

20 El Mass(M<sup>+</sup>) : 378

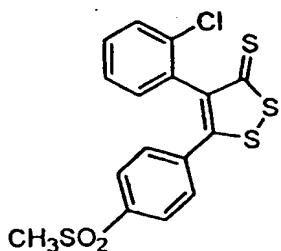
Melting point: 165-166°C

Example 57

4-(2-chlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione

25 e

Formula 61



210 mg (yield 68%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(2-chlorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

10  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  7.90(d, 2H,  $J=8.4\text{Hz}$ ), 7.53(d, 2H,  $J=8.4\text{Hz}$ ), 7.43(dd, 1H,  $J=9.2\text{Hz}$ ,  $J=1.6\text{Hz}$ ), 7.32(m, 2H), 7.12(dd, 1H,  $J=9.2\text{Hz}$ ,  $J=1.6\text{Hz}$ ), 3.05(s, 3H)

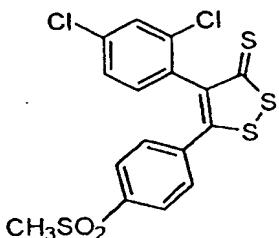
El Mass(M<sup>+</sup>) : 398

Melting point: 161-162°C

Example 58

15 4-(2,4-dichlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-t hione

Formula 62



198 mg (yield 64%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(2,4-dichlorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 7.94(d, 2H, J=8.4Hz), 7.50(d, 2H, J=8.4Hz), 7.43(s, 1H), 7.30(d, 1H, J=8.4Hz), 7.07(d, 1H, J=8.4Hz), 3.07(s, 3H)

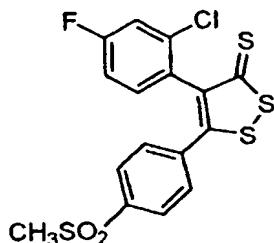
5 EI Mass(M<sup>+</sup>) : 433

Melting point: 176-177°C

Example 59

4-(2-chloro-4-fluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione

10 Formula 63



164 mg (yield 53%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(2-chloro-4-fluorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

15 <sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 7.83(d, 2H, J=8.4Hz), 7.43(d, 2H, J=8.4Hz), 7.07(dd, 1H, J=5.6Hz, J=2.4Hz), 7.03(dd, 1H, J=8.4Hz, J=6.0Hz), 6.93(td, 1H, J=6.0Hz, J=2.4Hz), 2.97(s, 3H)

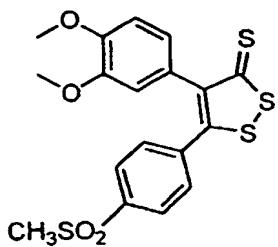
20 EI Mass(M<sup>+</sup>) : 416

Melting point: 184-185°C

Example 60

25 4-(3,4-dimethoxyphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione

Formula 64



155 mg (yield 50%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(3,4-dimethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

10  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  7.81(d, 2H,  $J=8.4\text{Hz}$ ), 7.40(d, 2H,  $J=8.4\text{Hz}$ ), 6.73(d, 1H,  $J=8.4\text{Hz}$ ), 6.61(d, 1H,  $J=2.0\text{Hz}$ ), 6.53(dd, 1H,  $J=7.2\text{Hz}, J=2.0\text{Hz}$ ), 3.78(s, 3H), 3.66(s, 3H), 2.96(s, 3H)

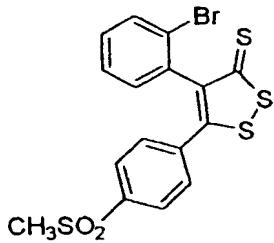
15 El Mass(M<sup>+</sup>) : 424

Melting point: 182-183°C

Example 61

15 4-(2-bromophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thio ne

Formula 65



186 mg (yield 60%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(2-bromophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 7.82(d, 2H, J=8.4Hz), 7.52-7.50(m, 1H), 7.46(d, 2H, J=8.4Hz), 7.25-7.23(m, 1H), 7.16-7.14(m, 1H), 7.01-7.00(m, 1H), 3.05(s, 3H)

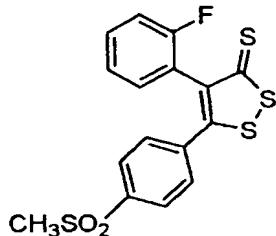
El Mass(M<sup>+</sup>) : 443

<sup>5</sup> Melting point: 179-180 °C

Example 62

4-(2-fluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thion

<sup>10</sup> e  
<sup>10</sup> Formula 66



<sup>15</sup> 170 mg (yield 55%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(2-fluorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

<sup>20</sup> <sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 7.82(d, 2H, J=8.4Hz), 7.42(d, 2H, J=8.4Hz), 7.30-7.29(m, 1H), 7.09-7.06(m, 2H), 6.94(t, 1H, J=9.3Hz), 3.05(s, 3H)

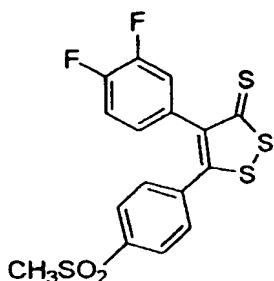
El Mass(M<sup>+</sup>) : 382

Melting point: 173-174 °C

Example 63

<sup>25</sup> 4-(2,4-difluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione

Formula 67



179 mg (yield 58%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(2,4-difluoro)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

10  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  7.85(d, 2H,  $J=8.4\text{Hz}$ ), 7.42(d, 2H,  $J=8.4\text{Hz}$ ), 7.12(dd, 1H,  $J=16.8\text{Hz}$ ,  $J=8.6\text{Hz}$ ), 6.87-6.84(m, 1H), 6.69-6.66(m, 1H), 3.0(s, 3H)

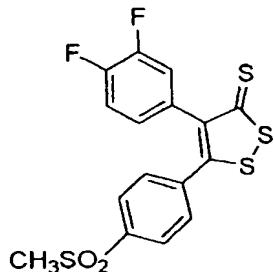
15 EI Mass(M $^+$ ) : 400

Melting point: 148-149°C

Example 64

15 4-(3,4-difluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-t  
hione

Formula 68



182 mg (yield 59%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(3,4-difluorophenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid

ethyl ester.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 7.86(d, 2H, J=8.4Hz), 7.38(d, 2H, J=8.4Hz), 7.05-7.01(m, 1H), 6.94-6.90(m, 1H), 6.74-6.72(m, 1H), 3.0(s, 3H)

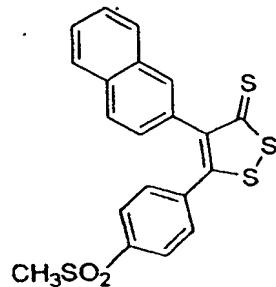
5 EI Mass(M<sup>+</sup>) : 400

Melting point: 193-194 °C

Example 65

5-(4-methanesulfonylphenyl)-4-(naphthalene-2-yl)-[1,2]dithiol-3-thi  
10 one

Formula 69



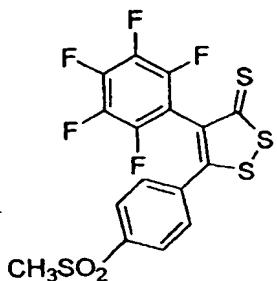
188 mg (yield 60%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 15 3-(4-methanesulfonylphenyl)-2-(naphthalene-2-yl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

19 1H-NMR(400MHz, CDCl<sub>3</sub>) δ 7.93(d, 2H, J=8.4Hz), 7.70-7.65(m, 6H), 7.37-7.35(m, 3H), 3.04(s, 3H)  
20 EI Mass(M<sup>+</sup>) : 414

Example 66

5-(4-methanesulfonylphenyl)-4-pentafluorophenyl-[1,2]dithiol-3-thi  
25 one

Formula 70



200 mg (yield 65%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-3-oxo-2-pentafluorophenyl-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

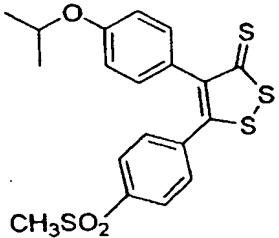
<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 8.07(d, 2H, *J*=8.4Hz), 7.26(d, 2H, *J*=8.4Hz), 3.13(s, 3H)

10 EI Mass(M<sup>+</sup>) : 454  
Melting point: 181-182 °C

### Example 67

4-(4-isopropoxylphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione

### Formula 71



210 mg (yield 68%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(4-isopropoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 7.90(d, 2H, J=8.4Hz), 7.47(d, 2H, J=8.4Hz), 7.06(d, 2H, J=8.8Hz), 6.84(d, 2H, J=8.8Hz), 4.52-4.50(m, 1H), 3.06(s, 3H), 1.32(s, 3H), 1.31(s, 3H)

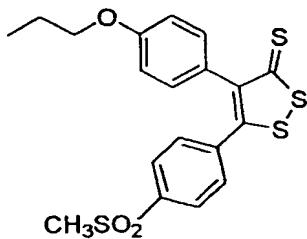
5 EI Mass(M<sup>+</sup>) : 422

Melting point: 179-180°C

Example 68

5-(4-methanesulfonylphenyl)-4-(4-propoxyphenyl)-[1,2]dithiol-3-thi  
one

10 Formula 72



207 mg (yield 67%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(4-methanesulfonylphenyl)-3-oxo-2-(4-propoxyphenyl)-propionic acid 15 ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

15 <sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 7.90(d, 2H, J=8.4Hz), 7.47(d, 2H, J=8.4Hz), 7.06(d, 2H, J=8.8Hz), 6.84(d, 2H, J=8.8Hz), 3.90(s, 3H), 3.05(s, 20 3H), 1.79-1.78(m, 2H), 1.19(t, 3H, J=8.0Hz)

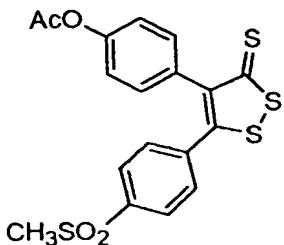
EI Mass(M<sup>+</sup>) : 422

Melting point: 177-178°C

Example 69

25 Acetic acid 4-[5-(4-methanesulfonylphenyl)-3-thioxo-3H-[1,2] dithiol-4-yl]phenyl ester

Formula 73



140 mg (yield 45%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(4-acetoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

10  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  7.92(d, 2H,  $J=9.4\text{Hz}$ ), 7.48(d, 2H,  $J=9.4\text{Hz}$ ), 7.19(d, 2H,  $J=7.6\text{Hz}$ ), 7.03(d, 2H,  $J=7.6\text{Hz}$ ), 3.08(s, 3H), 2.49(s, 3H)

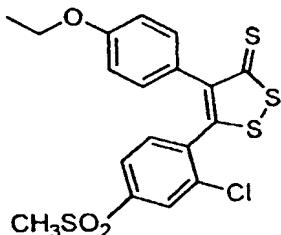
El Mass(M<sup>+</sup>) : 422

Melting point: 241-243°C

Example 70

15 5-(2-chloro-4-methanesulfonylphenyl)-4-(4-ethoxyphenyl)-[1,2]dithiol-3-thione

Formula 74



170 mg (yield 55%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(2-chloro-4-methanesulfonylphenyl)-2-(4-ethoxyphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

25  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  7.80(d, 1H,  $J=1.6\text{Hz}$ ), 7.69(dd, 1H,

*J*=6.4Hz, *J*=2.0Hz), 7.32(d, 1H, *J*=8.0Hz), 6.88(d, 2H, *J*=8.4Hz), 6.62(d, 2H, *J*=8.4Hz), 3.81(q, 2H, *J*=7.2Hz), 2.98(s, 2H), 1.23(t, 3H, *J*=4.0Hz)

El Mass(M<sup>+</sup>) : 443

Melting point: 190-191°C

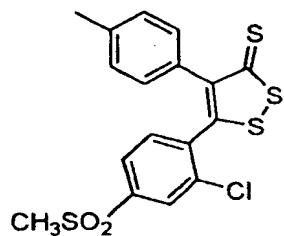
5

Example 71

5-(2-chloro-4-methanesulfonylphenyl)-4-p-toryl-[1,2]dithiol-3-thion

e

Formula 75



10

173 mg (yield 56%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(2-chloro-4-methanesulfonylphenyl)-3-oxo-2-p-toryl-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

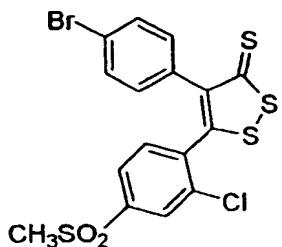
15 <sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 7.98(d, 1H, *J*=1.6Hz), 7.83(dd, 1H, *J*=6.0Hz, *J*=2.0Hz), 7.51(d, 1H, *J*=8.0Hz), 7.11(d, 2H, *J*=8.4Hz), 7.02(d, 2H, *J*=8.4Hz), 3.09(s, 3H), 2.32(s, 3H)

20 El Mass(M<sup>+</sup>) : 413

Melting point: 188-189°C

25 Example 72  
4-(4-bromophenyl)-5-(2-chloro-4-methanesulfonylphenyl)-[1,2]dithiol-3-thione

Formula 76



192 mg (yield 62%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 2-(4-bromophenyl)-3-(2-chloro-4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 7.98(d, 1H, J=1.6Hz), 7.86(dd, 1H, J=8.0Hz, J=1.6Hz), 7.51(d, 1H, J=8.0Hz), 7.11(d, 2H, J=8.4Hz), 7.02(d, 2H, J=8.4Hz), 3.09(s, 3H)

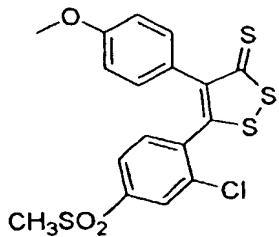
El Mass(M<sup>+</sup>) : 477

Melting point: 194-195 °C

### Example 73

15 5-(2-chloro-4-methanesulfonylphenyl)-4-(4-methoxyphenyl)-[1,2]dithiol-3-thione

### Formula 77



195 mg (yield 63%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.3 g of 3-(2-chloro-4-methanesulfonylphenyl)-2-(4-methoxyphenyl)-3-oxo-propionic acid instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 7.99(d, 1H, J=1.6Hz), 7.87(dd, 1H, J=8.0Hz, J=1.6Hz), 7.52(d, 1H, J=8.0Hz), 7.12(d, 2H, J=8.4Hz), 7.03(d, 2H, J=8.4Hz), 4.25(s, 3H), 3.09(s, 3H)

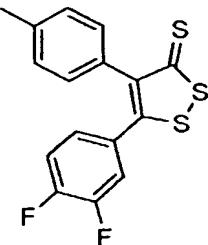
El Mass(M<sup>+</sup>) : 428

5 Melting point: 192-193°C

Example 74

5-(3,4-difluorophenyl)-4-p-toryl-[1,2]dithiol-3-thione

Formula 78



10

293 mg (yield 52%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.5 g of 3-(3,4-difluorophenyl)-3-oxo-2-p-toryl-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

15

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 7.15(d, 2H, J=7.6Hz), 7.03-7.01(m,3H), 6.98(d, 2H, J=7.6Hz), 2.33(s, 3H)

El Mass(M<sup>+</sup>) : 336

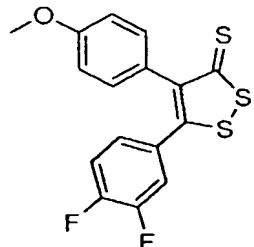
Melting point: 140-142°C

20

Example 75

5-(3,4-difluorophenyl)-4-(4-methoxyphenyl)-[1,2]dithiol-3-thione

Formula 79



25

274 mg (yield 52%) of the titled compound as a liquid was

prepared in the same manner as in Example 39 except using 0.5 g of 3-(3,4-difluorophenyl)-2-(4-methoxyphenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 7.16(d, 2H, J=7.6Hz), 7.04-7.02(m, 3H), 6.99(d, 2H, J=7.6Hz), 3.82(s, 3H)

El Mass(M<sup>+</sup>) : 352

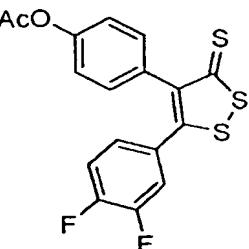
Melting point: 143-145°C

10

Example 76

Acetic acid 4-[5-(3,4-difluorophenyl)-3-thioxo-3H-[1,2]dithiol-4-yl]-phenyl ester

Formula 80



15

267 mg (yield 51%) of the titled compound as a liquid was prepared in the same manner as in Example 39 except using 0.5 g of 2-(4-acetoxyphenyl)-3-(3,4-difluorophenyl)-3-oxo-propionic acid ethyl ester instead of 2-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-3-oxo-propionic acid ethyl ester.

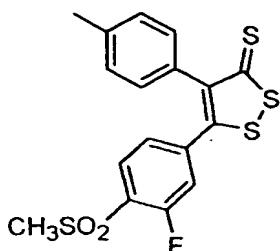
20 <sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 7.17(d, 2H, J=7.6Hz), 7.05-7.03(m, 3H), 6.99(d, 2H, J=7.6Hz), 2.32(s, 3H)

El Mass(M<sup>+</sup>) : 380

25 Melting point: 147-149°C

Example 77

5-(3-fluoro-4-methanesulfonylphenyl)-4-p-toryl-[1,2]dithiol-3-thione  
Formula 81



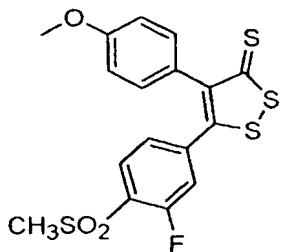
0.1 g of 5-(3,4-difluorophenyl)-4-p-toryl-[1,2]dithiol-3-thione which was prepared in the above example 74 was dissolved in dimethyl sulfoxide, and then 33 mg of sodium methanesulfinate was added thereto to let the mixture to react at 80°C for 3 hours. When the reaction was completed, the reaction mixtue was diluted with water and extracted with ethyl acetate. The obtained organic layer was dried on anhydrous magnesium sulfate and then purified by flash chromatography to give 66 mg of the titled compound as a red solid(yield 56%).

10          $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  7.90-7.89(m, 1H), 7.15-7.12(m, 4H), 7.00-6.98(m, 2H), 3.21(s, 3H), 2.34(s, 3H)  
           EI Mass(M<sup>+</sup>): 396  
           Melting point: 205-207 °C

15         Example 78

5-(3-fluoro-4-methanesulfonylphenyl)-4-(4-methoxyphenyl)-[1,2]dit  
       hiole-3-thione

Formula 82



20         58 mg (yield 50%) of the titled compound as a solid was prepared in the same manner as in Example 78 except using 5-(3,4-difluorophenyl)-4-(4-methoxyphenyl)-[1,2]dithiol-3-thione which was prepared in the above example 75 instead of 5-(3,4-difluorophenyl)-4-p-toryl-[1,2]dithiol-3-thione.

25          $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  7.85(t, 1H,  $J=1.2\text{Hz}$ ), 7.17(dd, 1H,

*J*=10.0Hz, *J*=2.0Hz), 7.15(dd, 1H, *J*=10.0Hz, *J*=2.0Hz), 6.96(d, 2H, *J*=8.8Hz), 6.84(d, 2H, *J*=8.8Hz), 3.74(s, 3H), 3.20(s, 3H)

El Mass(M<sup>+</sup>) : 352

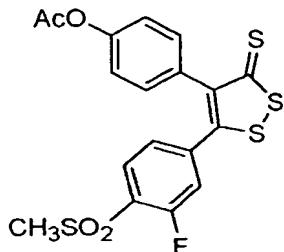
Melting point: 150-152°C

5

Example 79

Acetic acid 4-[5-(3-fluoro-4-methanesulfonylphenyl)-3-thioxo-3H-[1,2]dithiol-4-yl]-phenyl ester

Formula 83



10

60 mg (yield 52%) of the titled compound as a solid was prepared in the same manner as in Example 78 except using acetic acid 4-[5-(3,4-difluorophenyl)-3-thioxo-3H-[1,2]dithiol-4-yl]-phenyl ester which was prepared in the above example 76 instead of

15 5-(3,4-difluorophenyl)-4-p-toryl-[1,2]dithiol-3-thione.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 7.85(t, 1H, *J*=1.2Hz), 7.17-7.01(m, 4H), 6.92(d, 2H, *J*=8.0Hz), 3.14(s, 3H), 2.29(s, 3H)

El Mass(M<sup>+</sup>) : 440

Melting point: 200-201°C

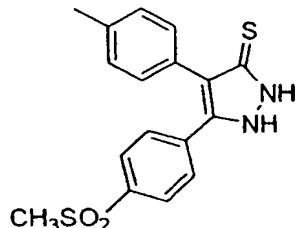
20

Example 80

5-(4-methanesulfonylphenyl)-4-p-toryl-[1,2]dihydropyrazole-3-thion

e

Formula 84



25

30 mg of potassium hydroxide was added to 0.1 g of 5-(4-methanesulfonylphenyl)-4-p-toryl-[1,2]dithiol-3-thione and then the mixture was dissolved in 5 ml of ethanol. Afterwards, 2 eq of hydrazine was added thereto to reflux at 80°C for 12 hours. The color change 5 from red to yellow was observed. Ethanol was distilled from the reacton mixture under reduced pressure, and the resultant was diluted with water and extracted with ethyl acetate. The obtained organic layer was dried on anhydrous magnesium sulfate to distill the solvent. The resultant was recrystallized with n-hexane to give 56 mg of the titled compound as 10 a yellow solid(yield 62%).

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 7.86(d, 2H, J=7.6Hz), 7.58(d, 2H, J=7.6Hz), 7.22(d, 2H, J=8.0Hz), 7.16(s, 2H, J=8.0Hz), 3.04(s, 3H), 2.38(s, 3H)

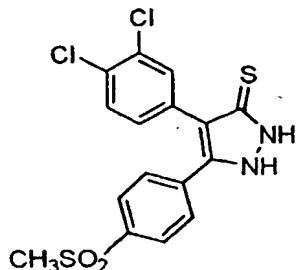
El Mass(M<sup>+</sup>): 344

15 Melting point: 198-200°C

Example 81

4-(3,4-dichlorophenyl)-5-(4-methanesulfonylphenyl)-1,2-dihydropyr 20 azole-3-thione

Formula 85



58 mg (yield 63%) of the titled compound as a liquid was prepared in the same manner as in Example 81 except using 0.1 g of 25 4-(3,4-dichlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione instead of 5-(4-methanesulfonylphenyl)-4-p-toryl-[1,2]dithiol-3-thione.

<sup>1</sup>H-NMR(400MHz, CDCl<sub>3</sub>) δ 7.83(d, 2H, J=8.0Hz), 7.58(d, 2H, J=8.0Hz), 7.50(d, 1H, J=8.0Hz), 7.16(s, 1H), 7.07(d, 1H, J=8.0Hz), 3.20(s, 3H)

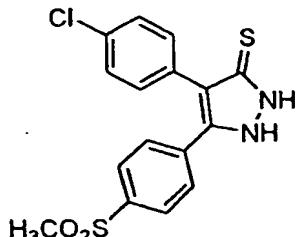
FAB Mass(M<sup>+</sup>1) : 399

30 Melting point: 192-193°C

Example 82

4-(4-chlorophenyl)-5-(4-methanesulfonylphenyl)-1,2-dihdropyrazole-3-thione

Formula 86



5

62 mg (yield 68%) of the titled compound as a liquid was prepared in the same manner as in Example 81 except using 0.1 g of 4-(4-chlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione instead of 5-(4-methanesulfonylphenyl)-4-p-toryl-[1,2]dithiol-3-thione.

10  $^1\text{H-NMR}$ (400MHz,  $\text{CDCl}_3$ )  $\delta$  7.80(d, 2H,  $J=8.0\text{Hz}$ ), 7.54(d, 2H,  $J=8.0\text{Hz}$ ), 7.42(d, 2H,  $J=8.4\text{Hz}$ ), 7.28(d, 2H,  $J=8.4\text{Hz}$ ), 3.19(s, 3H)

FAB Mass( $M+1$ ) : 365

Melting point: 211-213°C

15

Experiments1. Evaluation of selective COX-2 inhibitory activity1) Method

In order to pharmacologically determine the selective COX-2 inhibitory activity, the percentages of the COX-1 and COX-2 inhibition of the compounds of the present invention illustrated in the Examples were measured by the following methods.

a. Assay for the COX-1 inhibitory activity using U-937

25 U-937 human lymphoma cells (Korean Cell Line Bank, Seoul, Korea, Accession Number: 21593) were cultured and centrifuged. The collected cells were diluted with HBSS (x1, Hank's balanced salt solution) to a concentration of  $1 \times 10^6$  cells/ml. 1 ml of the dilute cell solution was placed into each well of 12-well plates. 5  $\mu\text{l}$  of 1  $\mu\text{M}$  solution of a test compound in DMSO and 5  $\mu\text{l}$  of DMSO as a control were added to the wells. The wells were incubated in  $\text{CO}_2$  incubator at

37°C for 15 minutes. Separately, 10 mM stock solution of arachidonic acid in ethanol was diluted ten times in ethanol to prepare 1 mM solution of arachidonic acid. Arachidonic acid acts as a substrate. 10  $\mu$ l of the 1 mM solution of arachidonic acid was added to each well and 5 incubated at CO<sub>2</sub> incubator at 37°C for 30 minutes. The cell solution of each well was placed in a centrifuge test tube and centrifuged at 10,000 rpm at 4°C for 5 minutes. The concentration of PGE2 in the collected cells and the supernatant was quantified by means of a monoclonal kit (Cayman Chemicals). The percentages of PGE2 inhibition in a group of 10 the test compound-treated cells in relation to a group of the DMSO-treated cells were calculated. Based on the calculated values, the COX-1 inhibitory activities were evaluated.

15 b. Assay for the COX-2 inhibitory activity using RAW 264.7 cell line

20 2  $\times$  10<sup>6</sup> cells of RAW 264.7 cell line (Korean Cell Line Bank, Seoul, Korea, Accession Number: 40071) were inoculated into each well of 12-well plates. Each well was treated with 250  $\mu$  M of aspirin and incubated at 37°C for 2 hours. After the culture media were replaced 25 with new culture media, the new culture media were treated with a test compound (30 nM) and incubated for 30 minutes. Then, each well was treated with interferon  $\gamma$  (100 units/ml) and lipopolysaccharide (LPS, 100 ng/ml) and incubated for 18 hours. The culture media were transferred to other test tubes. The concentration of PGE2 was quantified by means of the EIA kit (Cayman Chemicals).

2) Test results

30 The test results are presented in Table 1 below. The percentages of the COX inhibition were calculated according to the following equation:

% Inhibition = (concentration of PGE2 in test compound-untreated sample – concentration of PGE2 in test compound-treated sample) / (concentration of PGE2 in test compound-untreated sample)  $\times$  100

35

Table 1  
Cyclooxygenase (COX) Inhibition (%)

Samples	COX-1 (1 $\mu$ M)	COX-2 (30 nM)
Reference (Valdecoxib)	28.8	19
Example 39	15	36.6
Example 40	18.3	35.7
Example 41	20.1	24.5
Example 42	24.5	20.1
Example 43	19.3	38.4
Example 44	25.5	20.1
Example 45	19.6	22.1
Example 46	24.6	21.0
Example 47	22.5	21.4
Example 48	23.6	24.2
Example 49	28.0	19.5
Example 50	27.2	19.6
Example 51	27.6	19.8
Example 52	26.6	19.1
Example 53	26.7	21.6
Example 54	22.4	26.3
Example 55	27.6	20.2
Example 56	20.6	25.6
Example 57	20.7	21.1
Example 58	24.2	20.1
Example 59	23.2	19.7
Example 60	26.5	19.3
Example 61	23.3	20.1
Example 62	26.6	21.0
Example 63	20.3	21.3
Example 64	21.6	19.8
Example 65	22.6	20.1
Example 66	28.2	19.2
Example 67	27.5	23.3
Example 68	25.5	22.7
Example 69	24.8	21.3
Example 70	17.5	36.0
Example 71	20.3	21.0
Example 72	28.1	19.3
Example 73	25.6	20.1
Example 74	26.5	19.2
Example 75	26.6	19.6
Example 76	21.6	20.3
Example 77	15.2	31.5
Example 78	18.5	32.5
Example 79	19.5	30.2
Example 80	25.6	23.2

Example 81	24.9	24.6
Example 82	24.3	22.2

### 3) Evaluation

The *in vitro* test results about the percentages of the COX-1 and COX-2 inhibition are listed in Table 1.

As shown in Table 1, inhibition (%) ratios of COX-2 to COX-1 in 5 Examples 39 to 82 were significantly higher than that in the reference, Valdecoxib. This indicates that selective inhibition of COX-2 to COX-1 of the present compound is superior to that of the reference.

### Industrial Applicability

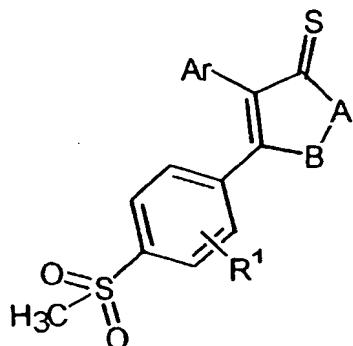
10 As apparent from the above description, the thione derivative according to the present invention is an alternative drug for conventional nonsteroidal antiinflammatory agents and is expected to be useful for treating patients with peptic ulcer disease, gastritis, regional enteritis, ulcerative colitis, diverticulitis, gastrorrhagia, osteoarthritis, or 15 rheumatoid arthritis.

While the present invention has been particularly shown and described with reference to exemplary embodiments thereof, it will be understood by those of ordinary skill in the art that various changes in form and details may be made therein without departing from the spirit 20 and scope of the present invention as defined by the following claims.

What is claimed is:

1. A thione derivative represented by formula 1:

Formula 1



5

wherein:

A and B each independently represent O, S, NR<sup>2</sup>; wherein R<sup>2</sup> represents hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkenyl, or aryl;

Ar represents aryl; heteroaryl; aryl or heteroaryl substituted with one to five radicals independently selected from the group consisting of C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, trifluoromethyl, nitro, acetoxy, amino, C<sub>1</sub>-C<sub>3</sub> alkylamino, C<sub>1</sub>-C<sub>3</sub> dialkylamino, hydroxy, C<sub>1</sub>-C<sub>3</sub> hydroxyalkyl, and thioxy; and

R<sup>1</sup> represents hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, cyano, nitro, hydroxy, amino, C<sub>1</sub>-C<sub>4</sub> alkylamino, or C<sub>1</sub>-C<sub>4</sub> dialkylamino; or a non-toxic salt thereof.

2. The thione derivative according to claim 1 wherein

A and B each independently represent S or NH;

Ar represents phenyl; phenyl substituted with one to five radicals independently selected from the group consisting of C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, halogen, trifluoromethyl, acetoxy, and nitro; pyridyl; or naphthyl;

R<sup>1</sup> represents hydrogen or halogen; or a non-toxic salt thereof.

25

3. The thione derivative according to claim 1 or claim 2, which is selected from the group consisting of:

4-(4-ethoxyphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thio

ne;

4-(4-bromophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thio

ne;

5-(4-methanesulfonylphenyl)-4-toryl-[1,2]dithiol-3-thione;

5-(4-methanesulfonylphenyl)-4-phenyl-[1,2]dithiol-3-thione;

5-(4-methanesulfonylphenyl)-4-methoxyphenyl-[1,2]dithiol-3-thion

e;

5-(4-methanesulfonylphenyl)-4-(2-trifluoromethylphenyl)-[1,2]dithio

l-3-thione;

10 4-(4-chlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thion

e;

4-(3,4-dichlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-t

hione;

5-(4-methanesulfonylphenyl)-4-pyridine-4-yl-[1,2]dithiol-3-thione;

15 5-(4-methanesulfonylphenyl)-4-pyridine-3-yl-[1,2]dithiol-3-thione;

5-(4-methanesulfonylphenyl)-4-pyridine-2-yl-[1,2]dithiol-3-thione;

4-(4-fluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thion

e;

4-(2,5-dimethoxyphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-

20 3-thione;

4-(3,5-dimethylphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-t

hione;

5-(4-methanesulfonylphenyl)-4-(3-methoxyphenyl)-[1,2]dithiol-3-thi

one;

25 5-(4-methanesulfonylphenyl)-4-(2-nitrophenyl)-[1,2]dithiol-3-thione

;

5-(4-methanesulfonylphenyl)-4-(3-trifluoromethylphenyl)-[1,2]dithio

l-3-thione;

5-(4-methanesulfonylphenyl)-4-o-toryl-[1,2]dithiol-3-thione;

30 4-(2-chlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thion

e;

4-(2,4-dichlorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-t

hione;

4-(2-chloro-4-fluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithi

ol-3-thione;

35 4-(3,4-dimethoxyphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-

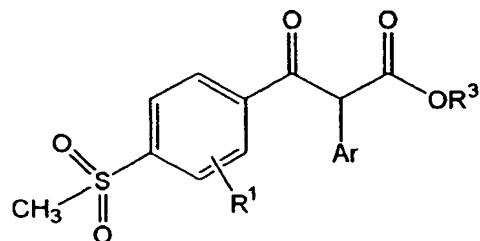
3-thione;

4-(2-bromophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;  
4-(2-fluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;  
5 4-(2,4-difluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;  
4-(3,4-difluorophenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;  
5-(4-methanesulfonylphenyl)-4-naphthalene-2-yl-[1,2]dithiol-3-thione;  
10 ne;  
5-(4-methanesulfonylphenyl)-4-pentafluorophenyl-[1,2]dithiol-3-thione;  
4-(4-isopropoxylphenyl)-5-(4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;  
15 5-(4-methanesulfonylphenyl)-4-(4-propoxyphenyl)-[1,2]dithiol-3-thione;  
acetic acid 4-[5-(4-methanesulfonylphenyl)-3-thioxo-3H-[1,2]dithiol-4-yl]phenyl ester;  
5-(2-chloro-4-methanesulfonylphenyl)-4-(4-ethoxyphenyl)-[1,2]dithiol-3-thione;  
20 5-(2-chloro-4-methanesulfonylphenyl)-4-p-toryl-[1,2]dithiol-3-thione;  
4-(4-bromophenyl)-5-(2-chloro-4-methanesulfonylphenyl)-[1,2]dithiol-3-thione;  
25 5-(2-chloro-4-methanesulfonylphenyl)-4-(4-methoxyphenyl)-[1,2]dithiol-3-thione;  
5-(3-fluoro-4-methanesulfonylphenyl)-4-p-toryl-[1,2]dithiol-3-thione;  
30 ;  
5-(3-fluoro-4-methanesulfonylphenyl)-4-(4-methoxyphenyl)-[1,2]dithiol-3-thione;  
acetic acid 4-[5-(3-fluoro-4-methanesulfonylphenyl)-3-thioxo-3H-[1,2]dithiol-4-yl]-phenyl ester;  
35 5-(4-methanesulfonylphenyl)-4-p-toryl-1,2-dihydropyrazole-3-thione;  
4-(3,4-dichlorophenyl)-5-(4-methanesulfonylphenyl)-1,2-dihydropyrazole-3-thione; and  
4-(4-chlorophenyl)-5-(4-methanesulfonylphenyl)-1,2-dihydropyrazole

le-3-thione  
or a non-toxic salt thereof.

4. A propionic acid derivative represented by formula 2:

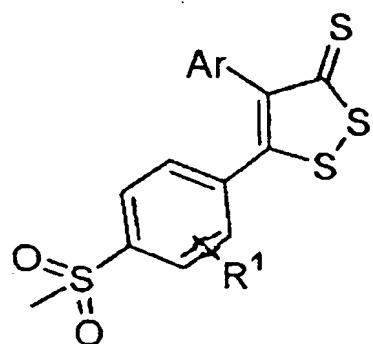
5 Formula 2



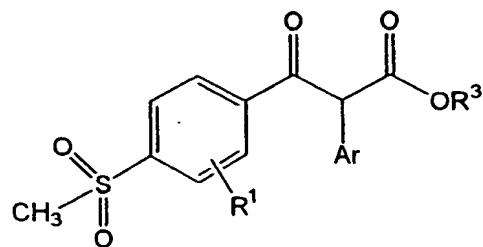
wherein, R<sup>1</sup> and Ar are as defined in claim 1 and R<sup>3</sup> represents C<sub>1</sub>-C<sub>4</sub> alkyl.

10 5. A method for preparing a thione derivative of formula 1a or a non-toxic salt thereof, comprising reacting a propionic acid derivative of formula 2 with phosphorus pentasulfide, Lawesson's Reagent, beta-oxothiocetic acid, or potassium beta-oxothiocetate:

15 Formula 1a



Formula 2



wherein:

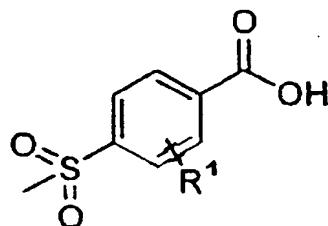
R<sup>1</sup> and Ar are as defined in claim 1;  
R<sup>3</sup> represents C<sub>1</sub>-C<sub>3</sub> alkyl.

5

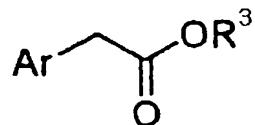
6. A method according to claim 5, wherein the propionic acid derivative of formula 2 is prepared by reacting a methanesulfonylbenzoic acid derivative of formula 3 with a aryl acetate derivative of formula 4 in the presence of a base;

10

Formula 3



Formula 4



wherein:

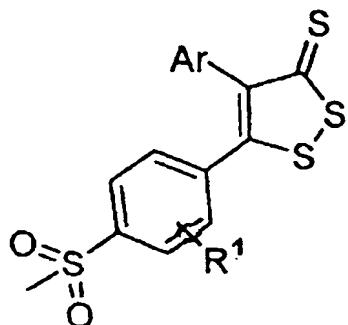
15

R<sup>1</sup> and Ar are as defined in claim 1 and R<sup>3</sup> represents C<sub>1</sub>-C<sub>4</sub> alkyl.

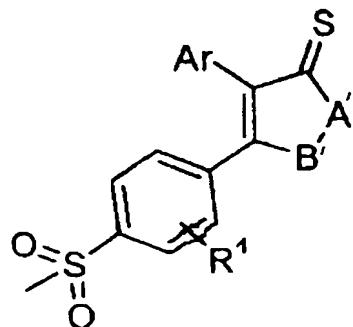
7. A method for preparing a thione derivative of formula 1b or a non-toxic salt thereof, comprising reacting a thione derivative of formula 1a with  $\text{NHR}^2\text{NH R}^2$  or  $\text{NH R}^2\text{OH}$  in the presence of a base;

5

Formula 1a



Formula 1b



wherein:

10 A' and B' each independently represent S or  $\text{NR}^2$ , provided that A' and B' are not simultaneously S; and  
 Ar and  $\text{R}^2$  are as defined in claim 1.

8. A pharmaceutical composition comprising a therapeutically effective amount of a thione derivative or a non-toxic salt thereof according to claim 1 to claim 3 as an active ingredient and a pharmaceutically acceptable carrier for the treatment of fever, pain, and inflammation.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/KR2003/002553

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 339/04

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
Korean patents and applications for inventions since 1975: IPC as aboveElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
CAPLUS, Delphion, Medline

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PARK J et al., "Screening of the anticancer potential of celecoxib and its derivatives" In Yakche Hakhoechi, 2003 JUNE, Vol. 33(2), pp 105-112 & CA 140:246247 see the whole document	1-3, 5-8
P, X	KR 2004-42246 A (CJ CORPORATION) 20 MAY 2004 see the whole document	1-8
A	US 5470871 A (LABORATOIRES DE THERAPEUTIQUE MODERNE) 28 NOVEMBER 1995 see the whole document	1-8
A	US 4760078 A (MITSUI TOATSU CHEMICALS INC.) 27 JULY 1988 see the whole document	1-8
A	SCHRJER DJ et al., "The pharmacologic effects of 5-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,4-thiadiazole-2(3H)-thione, choline salt (CI-986), a novel inhibitor of arachidonic acid metabolism in models of inflammation, analgesia and gastric irritation" In Prostaglandins, 1994, JANUARY, Vol. 47(1), pp 17-30 see the whole document	1-8

 Further documents are listed in the continuation of Box C. See patent family annex.

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Date of the actual completion of the international search

28 JULY 2004 (28.07.2004)

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**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

International application No.  
PCT/KR2003/002553

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US5470871A	28.11.1995	AU1768592A DE6920130201 DE69201302T2 EP0576619A1 ES2070002T3 FR2676057A1 HU65702A2 JP3226920B2 W09219613A2 ZA9203169A	21.12.1992 09.03.1995 28.09.1995 05.01.1994 16.05.1995 06.11.1992 28.07.1994 12.11.2001 12.11.1992 01.11.1993
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